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Epidemiology, Clinical Features and Outcomes of Patients with Sickle Cell Disease Hospitalized with Influenza

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EPIDEMIOLOGY, CLINICAL FEATURES AND OUTCOMES OF PATIENTS WITH SICKLE CELL DISEASE HOSPITALIZED WITH INFLUENZA

by

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ABSTRACT

Influenza is a respiratory viral infection responsible for annual epidemics, periodic pandemics and regularly causes substantial morbidity, mortality and economic burden worldwide. In the United States alone, influenza causes between 9.2 – 35.6 million cases, 140,000 to 710,000 hospitalizations and 12,000 – 56,000 deaths annually. Individuals with comorbid health conditions are at increased risk of hospitalization and severe outcomes from influenza infection and were recommended for vaccination prior to universal vaccine recommendations. Individuals with sickle cell disease (SCD) have been included in this group for decades though limited data existed to describe influenza among those with SCD. Recent studies showed pediatric patients with SCD were 56 times more likely to be admitted with influenza than those without SCD and may experience a greater risk of acute chest syndrome during illness though associated costs and outcomes were not worse among those with SCD. These studies were based on discharge data from short time periods and among pediatric patients. This study aims to describe the demographic and clinical features of patients of all ages admitted with lab-confirmed influenza across six seasons and assess their outcomes versus patients without SCD. Multivariable logistic regression models demonstrated patients with SCD had lower odds of ICU admission or pneumonia diagnosis during influenza-associated hospitalizations than individuals without SCD.

INDEX WORDS: Sickle cell disease, Influenza, Hospitalization, Surveillance, Epidemiology

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EPIDEMIOLOGY, CLINICAL FEATURES AND OUTCOMES OF PATIENTS WITH SICKLE-CELL DISEASE HOSPITALIZED WITH INFLUENZA

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DEDICATION

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CHAPTER 1

BACKGROUND AND SIGNIFICANCE

Introduction

Influenza is a common respiratory illness leading to between 9.2 and 35.6 million influenza cases, 140,000 and 720,000 hospitalizations and 12,000 to 56,000 influenza-related deaths in the United States alone (CDC, 2018a). Influenza and pneumonia rank as the eighth leading cause of death in the United States according to the Centers for Disease Control and Prevention (CDC) (CDC, 2017a). While everyone is at risk to develop an influenza infection, some individuals are at increased risk of complications such as hospitalization, pneumonia or death (Mertz et al., 2013). Groups at increased risk include individuals at the ends of the age spectrum (e.g., the very young, the elderly), as well as individuals with underlying medical conditions such as cardiac conditions, diabetes and other metabolic disorders, neurologic disorders, chronic respiratory conditions such as COPD or asthma, immunosuppression, chronic kidney disease, blood disorders, liver disorders, pregnancy, obesity and hemoglobinopathies such as sickle cell disease (SCD) (Bhat et al., 2005; Fiore et al., 2010; Izurieta et al., 2000; Keren et al., 2005; Louie et al., 2009; Miller et al., 2008; Neuzil, Wright, Mitchel, & Griffin, 2000; M. A. O'Brien et al., 2004).

Sickle cell disease is an inherited genetic disorder predominantly found among minority populations. Among Black/African-Americans, the incidence is approximately one in 365 live births and 1 in 16,300 among Hispanic-Americans (Hassell, 2010). The median life expectancy of someone born with SCD in 1973 was fourteen years (Diggs, 1973) but has increased to 40 – 60 years, still far short of the life expectancy of a non-SCD individual. Due to the increased life expectancy, it is estimated there are now approximately 100,000 individuals living in the United States with SCD (Hassell, 2010). Sickle cell disease is caused by genetic mutations affecting hemoglobin, the molecule responsible for transporting oxygen in the red blood cells throughout the body. Hemoglobin is malformed as a result of these mutations and in turn changes red blood cells from their normal round shape into crescents or sickles. These sickle-shaped cells can become stuck in blood vessel branches and capillaries resulting in reduction

or blockage of blood flow with distal ischemia or infarction which results in pain (e.g., sickle cell crisis). These crises adversely impact outcomes in patients with SCD.

Since the 1970s, the Centers for Disease Control and Prevention has considered people with SCD at increased risk of severe complications and adverse outcomes due to influenza. Despite the inclusion of SCD as a high-risk factor, studies have only recently begun to examine the interaction between influenza and SCD. One study demonstrated pediatric patients with SCD were hospitalized with influenza at a rate of 56 times greater than pediatric patients without SCD (Bundy, Strouse, Casella, & Miller, 2010). The rate of hospitalization for SCD patients with influenza was twice that of patients with cystic fibrosis (Bundy et al., 2010) another inherited genetic disorder found predominantly among Caucasians. A study of SCD pediatric patients in London during the 2009 H1N1 epidemic estimated that over 50% of children with SCD with influenza required hospitalization and over 25% developed Acute Chest Syndrome (ACS) (Inusa et al., 2010). This observed severity was consistent with another study indicating 2009 H1N1 infection caused worse outcomes than other seasonal influenza infections among patients with SCD (Strouse et al., 2010). Thus, the current data about influenza in patients with SCD are limited to small studies of short duration with limited patient data.

Sickle Cell Disease and Health Disparities

Due to the racial association of sickle cell disease, racial disparities must be examined and considered in the context of influenza and sickle cell disease. As of 2013, in the CDC Health Disparities and Inequalities Report, health disparities persisted or worsened for approximately 93% of Healthy People 2010 objectives (National Center for Health Statistics, 2012). The CDC describes health disparities as, “preventable differences in the burden of disease, injury, violence, or opportunities to achieve optimal health that are experienced by socially disadvantaged populations,” (CDC, 2008). Disadvantaged populations may be delineated by race, ethnicity, age, gender, socioeconomic status or several other characteristics.

Taken in its entirety, health disparity, even if one was to only consider race-related health disparities, it would likely be too broad a topic to discuss here. The discussion here will focus on health disparities in the context of individuals with sickle cell disease. SCD patients face disparities of two primary varieties; first in terms of access to medical care resources which contributes to the second type, the disparity in health outcomes.

According to Michael Debaun, director of the Vanderbilt-Meharry Center for Excellence in Sickle Cell Disease, there is a shortage of physicians prepared to treat SCD patients, particularly adult patients (Marcus, 2016). In addition to a shortage of physicians, only 1 in 5 family physicians reported feeling comfortable in treating people with SCD (Mainous et al., 2015) and 70% of family practitioners felt clinical decision tools would be helpful in the care of SCD patients (Kanter & Jordan, 2015). Physician shortages and knowledge gaps likely contribute to SCD patients experiencing difficulty transitioning to adult. During this time, young adults, 18-35 years old, with SCD must rely on emergency departments more frequently than older adults, over 35 years of age for care of SCD complications such as sickle cell pain and acute chest syndrome (K. Epstein, Yuen, Riggio, Ballas, & Moleski, 2006; Givens, Rutherford, Joshi, & Delaney, 2007). Patients with SCD experience 25% longer wait times in emergency departments than a general patient sample, a difference largely explained by the African-American race of SCD patients (Haywood, Tanabe, Naik, Beach, & Lanzkron, 2013). In the same study, it was also found that African-American patients with SCD experienced longer wait times than patients with long bone fractures even accounting for race and assigned triage level (Haywood et al., 2013).

The disparity in access to medical care results in decreased access to care and clinical interventions. Until 2017, only one drug was approved by the Food and Drug Administration for the treatment of sickle cell disease, hydroxyurea. Though hydroxyurea has been the recommended treatment for individuals suffering from frequent sickle cell pain or crisis, nearly 75% of adult patients do not receive hydroxyurea treatment (Stettler, McKiernan, Melin, Adejoro, & Walczak, 2015). Though the mortality rate decreased among children with SCD over the past few decades it has risen among adults (Haywood et al., 2013) and despite increased life expectancy among SCD patients over the past several

decades, the life expectancy of an individual with the most severe form of SCD is still 30 years shorter (Platt et al., 1994) than someone without SCD. Contributing to increased mortality among adults may be the difficulty in accessing proper medical care, particularly for young adults who experience increased mortality during this life stage (Quinn, Rogers, McCavit, & Buchanan, 2010). People with SCD experience high rates of hospital readmission within 30 days of discharge compared to patients without SCD (Elixhauser & Steiner, 2006) and the rate of stroke among adults aged 35-64 years of age is three times greater than among African Americans without SCD (Strouse, Lanzkron, & Urrutia, 2011).

Influenza-Associated Hospitalization Surveillance

Starting in 2003-04, CDC, in cooperation with state health departments and academic partners has been conducting active population-based surveillance for cases of laboratory-confirmed, hospitalized influenza under the Influenza-Associated Hospitalizations Surveillance program (FluSurv-NET) program. FluSurv-NET conducted surveillance among pediatric cases for two years and expanded surveillance to include all ages beginning in 2005-06. FluSurv-NET currently operates in thirteen states, includes 80 counties and municipalities covering a population of approximately 27 million people or roughly 9% of the US population. Surveillance data collected includes demographic data for each patient, symptoms at case presentation, comorbid conditions including sickle cell disease, bacterial and viral co-detections, clinical course and outcome. Influenza vaccination status and antiviral treatment for each case are also collected (Chaves, Lynfield, Lindegren, Bresee, & Finelli, 2015). Data is collected by trained surveillance officers using a standardized data collection tool.

Statement of the Problem

Current data suggest that children with SCD are at increased risk of influenza-associated hospitalization and potentially acute chest syndrome (Bundy et al., 2010) but their duration of hospitalization, hospitalization costs, and outcomes may not be worse than hospitalizations of children

without SCD. A different study of hospitalizations in London during the 2009 A/H1N1 pandemic yielded higher than expected influenza-related hospitalizations and acute chest syndrome among children with SCD (Inusa et al., 2010). Since individuals with SCD are living longer (Platt et al., 1994), it is important to understand the outcomes of SCD in both adults and children particularly within the context of disparities related to healthcare access and outcomes. Understanding the burden of disease, epidemiology, and outcomes of influenza infection in those with SCD could provide an opportunity to improve outcomes in this at-risk population through improved vaccination efforts, improved and/or earlier testing, and earlier antiviral administration. The FluSurv-NET surveillance project provides a unique opportunity to compare characteristics of SCD children and adults hospitalized with influenza with non-SCD patients.

Purpose Statement

This study aims to describe the demographic and clinical characteristics among individuals hospitalized with influenza with SCD compared to individuals hospitalized with influenza who do not have SCD. Of primary interest is determining whether individuals hospitalized due to influenza who have SCD experience more severe illness or suffer worse outcomes than individuals hospitalized with influenza who do not have SCD. Outcomes of interest that can be examined with the available data include admission to an ICU, mechanical ventilation requirement, discharge diagnosis of pneumonia or acute respiratory distress syndrome (ARDS) death and length of hospital stay. The study will also evaluate the frequency of influenza vaccination before hospital admission and anti-viral therapy during hospitalization among sickle cell patients compared to non-sickle cell patients as they may contribute to patient outcome and serve as indicators to determine whether SCD patients received an equivalent level of care as non-SCD patients.

Research Questions and Hypotheses

The primary objective of this study is to determine if SCD patients hospitalized with SCD have increased risk for severe outcomes compared to individuals without SCD. The ultimate outcomes of interest will be ICU admission and diagnosis of pneumonia at discharge. Preliminary data analysis will begin by describing and comparing the demographic characteristics of hospitalized influenza cases with and without SCD. Logistic regression models will be produced to assess the risk associated with SCD among patients hospitalized with influenza. Lastly, a secondary analysis will be conducted to compare non-respiratory and respiratory symptom frequency and frequency of other underlying comorbid conditions among patients hospitalized with influenza by SCD status. Presented below are the three main research questions with two null hypotheses stated for each.

Three research questions will be pursued and associated hypotheses tested, as listed below:

Research Question 1:

Among patients hospitalized with influenza, is there variation in intervention or treatment between patients with sickle-cell disease and those without sickle-cell diseases?

Null Hypothesis 1 – Among individuals hospitalized with laboratory-confirmed influenza, there is no difference in the proportion of patients that received influenza vaccine before hospital admission between patients with SCD and patients without SCD.

Null Hypothesis 2 – Among individuals hospitalized with laboratory-confirmed influenza, there is no difference in the proportion of patients that received antiviral treatment during hospitalizaiton between patients with SCD and patients without SCD.

Research Question 2:

Do individuals with SCD who are hospitalized with influenza have an increased risk of severe outcomes during hospitalization such as admission to an ICU or diagnosis of pneumonia compared to individuals without SCD hospitalized with influenza?

Null Hypothesis 3 – Among individuals hospitalized with laboratory-confirmed influenza, there is no difference in the odds of ICU admission between patients with SCD and patients without SCD.

Null Hypothesis 4 – Among individuals hospitalized with laboratory-confirmed influenza, there is no difference in the odds of pneumonia diagnosis between patients with SCD and patients without SCD.

A parallel analysis of the above hypotheses will also be conducted limiting the data to African-American individuals to assess the quality of care among African American SCD patients in comparison to African-American patients without SCD.

A secondary analysis will be performed to describe and compare respiratory and non-respiratory symptoms preceding influenza-related hospitalization between individuals with and without SCD. A comparison of underlying comorbid conditions will also be performed. The hypotheses for the secondary analysis are listed below.

Research Question 3:

Among patients hospitalized with influenza, are there differences in clinical symptoms at presentation and comorbid underlying conditions between patients with sickle-cell disease and those without sickle-cell disease hospitalized with influenza?

Hypothesis 5 – Among individuals hospitalized with laboratory-confirmed influenza, there is no difference in the proportion of patients that reported respiratory or non-respiratory symptoms between patient with SCD and patients without SCD.

Hypothesis 6 – Among individuals hospitalized with laboratory-confirmed influenza, there is no difference in the proportion of patients with underlying comorbid medical conditions between patients with SCD and patients without SCD.

Delimitations

The study was delimited to a previously generated, secondary dataset derived from population-based surveillance for laboratory-confirmed, hospitalized cases of influenza from a designated catchment area summarized in Table 1. Included in the catchment area are 14 study sites from 13 states encompassing 79 counties or municipalities representing nearly 28 million people based on 2015 population estimates or approximately 8.5% of the US population. Table 1 summarizes the FluSurv-NET catchment area and the estimated population of each area in 2015. The study here focuses on data analysis of the previously available dataset spanning 6 influenza seasons. Variables of interest for the analysis include, patient demographics (age, sex, race and ethnicity), underlying comorbid conditions, co-infections (bacterial or viral), anti-viral treatment, influenza vaccine status prior to hospitalization, clinical course (number of days hospitalized, ICU admission, mechanical ventilation required, abnormal x-ray), discharge diagnoses (physician stated and ICD codes) and outcome status (dead or alive).

Significance of the Study

Annually, influenza causes substantial morbidity, mortality and financial burden domestically and worldwide (Molinari et al., 2007). CDC estimates influenza has caused between 9.2 – 35.6 million cases,

140,000 to 710,000 hospitalizations and 12,000 – 56,000 deaths annually in the United States since 2010 (CDC, 2018a).

In 2002, the National Institute of Health (NIH) released the fourth edition of The Management of Sickle Cell Disease. The original was published in 1984 with revisions in 1989 and 1995 and a reprint in 1999. This resource covered several broad areas including Diagnosis and Counseling, Health Maintenance, Treatment of Acute and Chronic Complications and a section for Special Topics (NIH, 2002). In terms of influenza, the only guidance included in the document was the following, "Viral influenza infections can cause severe morbidity in individuals with SCD. Yearly vaccination recommendations should be followed, (NIH, 2002, pg. 75). Considering it has been shown that in more than half the instances of Acute Chest Syndrome an infectious agent is present and 12% of the time this agent is a virus, the guidance is highly limited.

NIH issued a new report in 2014 titled Evidence-Based Management of Sickle Cell Disease, Expert Panel Report(Yawn et al., 2014). Planning for this report began in 2009, the same year a novel strain of influenza emerged, spread across the world and became the most recent global influenza pandemic since the Hong Kong H3N2 pandemic in 1968 (Kilbourne, 2006). Despite recent studies published since 2009 indicating influenza contributes substantial burden among the sickle cell disease population resulting in significant hospitalizations, no mention of influenza appears in this publication at all.

The lack of vaccine recommendation runs counter to recommendations by the Committee on Infectious Diseases of the American Academy of Pediatrics and the Advisory Committee on Immunization Practices (ACIP). Both organizations endorsed recommendations of annual influenza immunization among individuals with sickle cell disease and other hemoglobinopathies in 1986 and 1989 respectively ("Prevention and control of influenza: Part I, Vaccines," 1989; Rice, 1986). Despite current universal influenza vaccine recommendations, the inconsistency of past recommendations is consistent with deficiencies in coordinated care of SCD patients as pointed out previously, "There is uneven availability and utilization of multidisciplinary specialty clinics for different genetic diseases. For 2

disorders (i.e., hemophilia and cystic fibrosis), effective national networks of specialty clinics exist and reach large proportions of the target populations. For other disorders, notably, sickle cell disease, fewer such centers are available, centers are less likely to be networked, and centers are used less widely" (Grosse et al., 2009).

This study was conducted to better understand the presentation, and course of influenza illness and effect of healthcare intervention including vaccination and antiviral treatment among individuals who have SCD with the intent of making better prevention and treatment recommendations related to reducing morbidity and mortality due to influenza.

Limited epidemiologic data exist on host characteristics, clinical features, and outcomes of sickle cell disease patients hospitalized with influenza in the United States or worldwide. Understanding these areas could provide insight into ways to improve influenza vaccination, diagnosis, and treatment among individuals with sickle cell disease.

Definition of Terms

Active surveillance: Stimulus provided to healthcare workers to prompt reporting to public health.

Adult influenza patient: Any subject identified in the surveillance system that is 18 years of age or older at the time of admission to hospital.

Antiviral Treatment: The patient received at least one dose of antiviral medication including oseltamivir, zanamivir, amantadine or rimantadine.

Asthma: Asthma or Reactive Airways Disease present in participants.

Cardiovascular Disease: Atherosclerotic cardiovascular disease, atrial fibrillation, cerebral vascular accident/stroke, congenital heart disease, coronary heart disease (CAD), congestive heart failure (CHF) or other unspecified cardiovascular disease reported in patient's chart as an underlying medical condition.

Chronic Lung Disease: Cystic Fibrosis, emphysema or chronic obstructive pulmonary disorder (COPD) or another unspecified chronic lung disorder identified as a comorbid medical condition during chart abstraction.

Diabetes: Type I or II diabetes present study subject

Extracorporeal mechanical oxygenation (ECMO): Treatment used for patients experiencing respiratory failure. The patient's blood is pumped out of their body and through an artificial lung to exchange carbon dioxide for oxygen. The blood is then pumped back into the patient.

Health Disparity: The preventable differences in the burden of disease, injury, violence, or opportunities to achieve optimal health that are experienced by socially disadvantaged populations.

Hospitalized patient: A patient admitted to a catchment area hospital floor or ward or a patient who spent more than 24 hours combined in an emergency department and observation ward/clinical decision unit (CDU).

ICU admission: Includes admission an intensive care unit including but not limited to neonatal ICU, pediatric ICU, surgical ICU, medical ICU or cardiac ICU for any amount of time during hospitalization.

Immunocompromised: Patient was identified to have HIV infection, AIDS, cancer diagnosis or treatment in 12 months before admission, complement deficiency, immunoglobulin, deficiency, immunosuppressive therapy, organ transplant, stem cell transplant, and steroid therapy in 2 weeks before admission or another unspecified immunocompromising condition during medical chart abstraction.

Immunized/vaccinated patient: An individual who has received either trivalent or quadrivalent influenza vaccine since August 1st of the respective season of hospitalization and at least 14 days before their date of admission to the hospital.

Influenza: An infectious respiratory illness and the viruses which cause it.

Influenza-like illness: Individuals presenting with the symptoms of cough or sore throat in the presence of fever greater than or equal to 100 °F.

Laboratory-confirmed influenza: A case of influenza confirmed by an acceptable influenza diagnostic test and not solely based on clinical symptom observation. Typical laboratory tests include rapid influenza diagnostic tests and reverse transcriptase-polymerase chain reaction (RT-PCR).

Mechanical Ventilation: Invasive, ventilator assisted breathing support for individuals experiencing respiratory failure.

Neuromuscular disorder: The patient had Duchenne muscular dystrophy, muscular dystrophy, multiple sclerosis, mitochondrial disorder, myasthenia gravis or another unspecified neuromuscular disorder listed in their medical chart as an underlying comorbid condition.

Neurologic disorder: Cerebral palsy, cognitive dysfunction, dementia, developmental delay, Down syndrome, plegia, paralysis, seizure disorder, or another unspecified neurologic condition identified during medical chart abstraction.

Obese: BMI was greater than or equal to 30 or obesity was stated by a physician in the medical chart in the absence of a recorded or calculated BMI score.

Pediatric patient: Any subject identified in the surveillance system that is younger than 18 years of age at the time of hospital admission.

Pneumonia: An inflammation of lung tissue typically caused by an infectious agent.

Population-based surveillance: Surveillance system designed to detect all cases in a given population to produce accurate disease rates.

Renal Disease: Patients were determined to have a renal disease if any of the following conditions were identified during chart abstraction: chronic kidney disease (CKD), chronic renal insufficiency, end-stage renal disease (ESRD), dialysis, glomerulonephritis, nephrotic syndrome or another unspecified renal condition.

Sickle Cell Disease: This pertains to a collection of inherited, genetic disorders that cause abnormal hemoglobin, the protein found in red blood cells responsible for oxygen delivery to cells. In SCD, hemoglobin proteins are folded differently and result in misshapen red blood cells leading to multiple

downstream repercussions such as anemia, increased risk of infection, chronic pain and other complications.

CHAPTER 2

LITERATURE REVIEW

Influenza Virology

Influenza pertains both to a collection of viruses, A through D, and to the upper respiratory illness caused by infection with one of the viruses (WHO, 2018) (Hause et al., 2014). Humans may become infected with three influenza types including A, B and C (Longo, 2012) though types A and B are most clinically relevant to humans causing annual epidemics (Pleschka, 2013). Infection with influenza ranges from mild to severe and may cause prolonged illness, hospitalization resulting in severe morbidity and even death and (W. W. Thompson et al., 2003). Influenza C causes a mild infection and is not believed to cause annual epidemics and therefore will not be considered further. Influenza A may also infect avian and swine populations resulting in substantial agricultural relevance which is beyond the scope of this discussion (Çakır, Boland, & Wang, 2017). However, it is this ability that makes influenza A of substantial clinical and public health importance since it allows influenza A to cause periodic pandemics potentially causing significant health and financial burden (Meltzer, Cox, & Fukuda, 1999; Molinari et al., 2007).

Influenza A may be further divided into subtypes based on the combinations of different variations of two surface proteins; hemagglutinin and neuraminidase. Eighteen hemagglutinin types exist while there are 11 neuraminidase variations. Beyond subtypes, influenza A is further broken down into strains that would, for instance, distinguish between the H1N1 strain of seasonal influenza that was in circulation before 2009 and the novel strain that emerged that year to cause a pandemic. Influenza B does not have subtypes but began diverging into two distinct lineages in the 1970s and are named after their first representatives, Yamagata and Victoria (Rota et al., 1990).

The timing of influenza season varies from year to year though influenza does circulate year-round and cases are observed in summer months. In the Northern Hemisphere, the influenza season is typically mid-fall to early spring with a seasonal activity peak between October and March (CDC, 2018c). FluSurv-NET has observed influenza activity in late April and into May in recent seasons (unpublished

EIP data) and the 2009 H1N1 pandemic began in April and peaked on the west coast study sites in late spring and summer of that season. In response to the pandemic, FluSurv-NET continued influenza surveillance throughout the summer of 2009 to observe and characterize as many pandemic cases as possible. The Southern Hemisphere influenza season occurs during the opposite time of year from the Northern hemisphere running from May through October (Sullivan, Pennington, Raupach, Franklin, Bareja, de Kluyver and the National Influenza Surveillance Committee, for the Communicable Diseases Network Australia, 2015). An influenza season in one hemisphere can provide insight and is used to predict and select vaccine strains for the upcoming influenza season in the opposing hemisphere and vaccines formulations are selected and produced twice each year (WHO, 2012). Despite this, influenza seasons can be difficult to predict and as has been said, "the only thing predictable about flu is that it is unpredictable (Anderson, Evan, 2017)."

Naturally, the next question is what makes influenza so unpredictable? To answer this question will require an examination of the nature of the influenza viruses. The typical culprit is influenza A and is the result of a couple of key characteristics. First, it can infect multiple host species, most notably humans, swine and avian hosts. Influenza B on the other hand only infects humans (CDC, 2017c). Another key differentiating feature between influenza A and B is influenza A mutates approximately 2 to 3 times faster than influenza B (Nobusawa & Sato, 2006). Mutation of influenza viruses occurs via two distinct mechanisms, antigenic drift and antigenic shift which may also be called reassortment (Taubenberger & Kash, 2010).

Before proceeding though, a discussion of the involved, surface proteins responsible for viral binding and release is in order. Hemagglutinin and neuraminidase are influenza membrane glycoproteins that play critical roles in influenza infection and propagation. Hemagglutinin is responsible for the binding of influenza to sialic acids to carbohydrate side-chains of cellular glycoproteins facilitate cell infection (Sauter et al., 1989). Following infection and during replication, neuraminidase cleaves sialic acid from cellular and viral glycoproteins to prevent aggregation of new viruses and allowing release from infected cells to infect other cells (Liu, Eichelberger, Compans, & Air, 1995; Palese, Tobita, Ueda,

& Compans, 1974). The immune response by hosts is typically directed against these two surface proteins.

Antigenic drift occurs as frequent, nearly constant, point mutations during viral replication in the genes that encode for hemagglutinin and neuraminidase. Influenza A and B both exhibit antigenic drift and may yield selective advantages in some strains allowing them to evade previous host immunity (Taubenberger & Kash, 2010).

Antigenic shift, on the other hand, happens by an entirely different process from antigenic drift and is specific to influenza A. The genomes of influenza A & B are divided into eight, single-stranded ribonucleic acid (RNA) fragments. Antigenic shift or reassortment occurs when a person or an animal becomes infected by two or more different influenza A viruses. Each new viral particle released contains one of each of the eight genome segments. In a host infected by multiple viruses, each RNA fragment can come from a different virus resulting in a novel influenza subtype with the capacity to cause a pandemic and substantial morbidity and mortality. The most recent influenza pandemic in 2009 was caused by reassortment and the new subtype contained RNA fragments from three previous influenza subtypes; one human, one swine and one avian. In the past century, nearly twenty influenza A reassortants have emerged with half a dozen of these capable of efficient human-to-human transmission (Bui, Chughtai, Adam, & MacIntyre, 2017). Of particular note, the rate of emergence of novel influenza strains has increased in recent years which may be due in part to better zoonotic surveillance, a real increase in novel strain emergence (Bui et al., 2017).

Influenza Symptoms and Complications

The illness caused by influenza viruses is often referred to simply as "the flu." The severity of illness and presentation of symptoms varies substantially from person to person. In mild cases, influenza may present similarly to more common colds though influenza often differs from colds due to its rapid onset. Typical symptoms experienced in mild cases of influenza include some or all of the following:

fever/chills, cough, sore throat, nasal congestion or rhinorrhea, muscle or body aches, headaches, and fatigue. Vomiting and diarrhea may occur in some individuals though more commonly observed in children than in adults (CDC, 2017b). Emergency symptoms warranting immediate clinical care and intervention differ between children and adults. Severe influenza infection in adults may result in difficulty breathing or shortness of breath (SOB), dizziness, chest pain, confusion or altered mental status (Cox & Subbarao, 1999). In children, particularly those too young to accurately relay symptoms, signs indicative of severe influenza illness are rapid or troubled breathing which may include wheezing or retractions while breathing, cyanosis (blue skin color), not drinking sufficient fluids, increased irritability, fever with rash, inability to eat, lack of tears when crying or flu-like symptoms that improve but then return with fever and more severe cough (CDC, 2017b).

Influenza Transmission

Influenza viruses can be highly contagious and are transmitted primarily through person to person contact. Droplets formed when infected individuals speak, sneeze or cough are believed to be the principal route of transmission and may be transferred up to approximately six feet away when droplets land in the mouths or noses of individuals nearby an infected individual. A less important route of transmission is from contaminated surfaces when an uninfected individual picks up viral particles from the environment after an infected person has shed the virus (CDC, 2018b). Once exposed, symptoms typically begin within a couple days but may present between one to four days post-exposure. Adults can be infectious for approximately one day before symptom onset and up to a week after symptoms emerge (CDC, 2018b) while children shed influenza virus for a longer time than adults (Li et al., 2010; To et al., 2010).

Morbidity and mortality due to influenza infections are strongly age-dependent affecting the very young, under 5 years of age, and the very old, sixty-five years and older, at rates substantially higher than individuals in between. Typically, 5-17 year old pediatric patients have the lowest rates of infection and

complications from influenza and the burden increases in adults as age increases. However, during the 2009 H1N1 pandemic, there was a greater burden among individuals less than 65 years of age than usual (Dawood et al., 2012). Since the most recent influenza pandemic, two A subtypes have been in circulation, the (H1N1) pdm2009 and an H3N2 subtype which has been in circulation since 1968 (Kilbourne, 2006). Over the past several seasons, these two subtypes have exchanged predominance annually. During seasons where H3N2 has been the predominant subtype the burden in adults sixty-five years and older has been substantially greater than years when 2009 H1N1 was the predominant influenza A subtype circulating (Simonsen et al., 1997). Influenza B causes disproportionate burden in pediatric populations though infections among adults are observed. Influenza B normally circulates later than influenza A though in some recent years circulation of influenza B has been observed throughout influenza seasons.

Influenza Burden

The burden of influenza differs significantly from season to season depending on the predominant strains circulating, the proportion of susceptible individuals, the effectiveness of the current vaccine and the amount of vaccine uptake. Annual influenza epidemics may infect up to 20% of the population (W. W. Thompson et al., 2003). Current studies and models by CDC estimate there to be between 9.2 and 35.6 million cases of influenza, 140,000 to 710,000 influenza-related hospitalizations and 12,000 to 56,000 influenza-related deaths each year in the United States (CDC, 2018a).

Individuals with underlying health conditions are at an increased risk of influenza infection, influenza-related hospitalizations, severe outcomes and death depending on the comorbid condition (Mertz et al., 2013). Predisposing comorbidities include cardiac conditions, diabetes, neurologic disorders, chronic respiratory conditions such as COPD or asthma, immunosuppression, chronic kidney disease, blood disorders or hemoglobinopathies such as sickle cell disease, metabolic disorders, liver disorders, pregnancy, and obesity (Bhat et al., 2005; Fiore et al., 2010; Izurieta et al., 2000; Keren et al.,

2005; Louie et al., 2009; Miller et al., 2008; Neuzil et al., 2000; M. A. O'Brien et al., 2004). Even if vaccinated, obese individuals have an increased risk of developing influenza or influenza-like illness compared to vaccinated healthy weight individuals (Neidich et al., 2017).

Influenza Vaccine

The first inactivated influenza vaccine was licensed in the United States in 1945 (Weir & Gruber, 2016). From 1945 until 1978, most vaccines available in the United States were monovalent or bivalent. Since 1978, most influenza vaccines offered have been trivalent and contained two circulating influenza A types and one influenza B type. In the last couple of years, quadrivalent influenza vaccines have emerged designed to protect against two influenza A types and two influenza B lineages. In 2003, a live attenuated influenza vaccine (LAIV) was licensed that could be delivered as a nasal mist instead of injection and has been available since then. The ACIP did not recommend the use of the LAIV in the 2016-17 season as it was shown to not be effective. Nevertheless, in the 2016-17 influenza season at least a dozen influenza vaccines were on the market including trivalent inactivated vaccines, quadrivalent inactivated vaccines and a high-dose vaccine designed for individuals 65 years and older who may not have a strong enough immune response to a normal dose vaccine (CDC, 2018d). Monovalent vaccines have been produced on an as-needed basis such as during the 2009 H1N1 pandemic.

In March 2013, CDC released a report on pediatric influenza-related deaths. To that point in the season, there were over 100 pediatric influenza deaths reported to CDC and approximately 90% of them were not vaccinated (CDC, 2013). Influenza vaccines have been demonstrated to prevent infection, ameliorate breakthrough infections and reduce influenza-related mortality and the annual influenza vaccine is considered the best method to prevent influenza-associated illness, hospitalizations and death (Barker & Mullooly, 1980; Fedson et al., 1993; Gross et al., 1988; Nichol, Margolis, Wuorenma, & Von Sternberg, 1994).

The effectiveness of the seasonal influenza vaccine can vary substantially. Since the 2004-05 influenza season, the estimated effectiveness of the influenza vaccine ranges from 10% effectiveness in 2004-05 to 60% during the 2010-11 season. A pair of EIP studies demonstrated that even when influenza vaccination does not prevent hospital admission it attenuates the course of illness and reduces severity in adults (C. Arriola et al., 2017; C. S. Arriola et al., 2015). The first study analyzed data from the 2012-13 influenza season where there was an indication of reduced severe illness among individuals who were vaccinated due to shorter ICU stays among younger adults, 18-49 years of age. The second study was more definitive and demonstrated decreased rates of ICU admission among adults 50 years and older, shorter hospital and ICU stay duration in adults 50 years and older and decreased odds of death from influenza in all adult ages.

Respiratory illnesses are common among children and caused by a variety of viruses and bacteria notably respiratory syncytial virus and influenza (Munoz, 2002). The rate of outpatient visits and hospitalizations can be quite high among healthy and high-risk children (M. A. O'Brien et al., 2004). In this study, it was found healthy children 6 months to 23 months of age had a rate of 14.5outpatient visits per person-month and a rate of 10.4 hospitalizations per 10,000 person-years. Children categorized as high-risk for complications from influenza were found to have an outpatient visit rate nearly double at 28.7 visits per 100-person months and a rate of hospitalization over four times greater than healthy children of 44.6 hospitalizations per 10,000 person-years.

The high-risk category included children with several previously diagnosed comorbidities in the preceding twelve months including cardiopulmonary illness, malignancies, cystic fibrosis, immune deficiencies, hereditary hemolytic anemias including SCD and an assortment of other underlying conditions. It had been demonstrated in multiple studies that children with certain underlying conditions were at increased risk of hospitalization due to influenza (Glezen, Greenberg, Atmar, Piedra, & Couch, 2000; Neuzil et al., 2000) or that influenza infection led to excess morbidity. Unfortunately, it was an aggregate comparison and did not determine hospitalization rates as a result of influenza among children with specific underlying conditions.

In London, during the 2009 A (H1N1) pandemic pediatric admissions were assessed to determine the frequency of sickle cell disease among those admitted. Approximately 2200 patients with SCD were seen at the reporting hospitals. Between April and August of 2009, 21 of the 2200 SCD patients sought care at a hospital due to influenza infection. Based on attack rates of the 2009 A(H1N1) strain of influenza it was estimated there should have been 40 cases of influenza among the 2200 patients registered with SCD. The implication is over half (21 of the 40 expected cases) required hospitalization and one quarter (10) developed acute chest syndrome. This is a high rate of complication and hospitalization among individuals with SCD compared to the expected rate of hospitalization and complication among the general population (Inusa et al., 2010). Furthering the discussion, Inusa et al. pointed out an influenza pandemic could be especially bad in Africa where most children with SCD live and often lack ready access to vaccination, antibiotics, transfusions, and other supportive medical care.

Variation in the influenza vaccine may have undertones of health inequities and social determinants. Increased education and income were both associated with increased influenza vaccine uptake (Linn, Guralnik, & Patel, 2010). BRFSS also demonstrated higher vaccine coverage rates among individuals with underlying conditions including an increased vaccine coverage rate among individuals with two or more high-risk diseases than individuals with only one high-risk condition (Linn et al., 2010).

Influenza and Racial Disparity

In 1999, influenza and pneumonia were the 7th leading cause of death in the United States but by 2010 influenza and pneumonia had fallen to the 9th leading cause of death (Chang, Moonesinghe, Athar, & Truman, 2016). At both time points, the mortality rate among non-Hispanic blacks was greater than among non-Hispanic whites though the discrepancy did decrease during the decade under study. American Indians or Alaskan Natives had the highest mortality due to influenza and pneumonia in both years assessed.

Mortality rates of influenza and pneumonia vary between urban and rural settings. The mortality rate from influenza and pneumonia has been slightly higher in rural communities over the past few decades. In 1990-1992 the rates were 34.38 vs. 35.65 for urban and rural areas respectively. By 2005-2009 the mortality rates had decreased in both areas to 17.05 and 19.72 but the discrepancy between urban and rural settings had grown; rate ratio of 1.04 in the earlier period and 1.16 in 2005-2009. If one compares affluent metro / urban areas to poor rural settings the disparity has grown even more between 1990-1992 and 2005-2009. In 1990-1992, the disparity between affluent metro areas and poor rural areas was modest, 33.34 vs. 36.76 respectively with a rate ratio of 1.10. The rate ratio in 2005-2009 was 1.53 though the mortality rates in both locations had decreased substantially, 15.12 and 23.14 for affluent urban and poor rural areas respectively (Singh & Siahpush, 2014).

In an analysis of FluSurv-NET data from New Haven, CT, the rates of hospitalization related to influenza among children under five were found to be substantially higher among minority populations compared to white children. Black children were hospitalized at a rate of 3.4 times more than white children while Hispanic children were hospitalized at a rate 3.0 times greater than white (Yousey-Hindes & Hadler, 2011). Using geospatial analysis by linking influenza cases to Census Tract data, the authors further demonstrated poverty and neighborhood crowding as independent predictors of hospitalization due to influenza. Annual incidence rates for hospitalization among children living in high-poverty and high-crowding census tracts were at least 3 times greater than children living in low-poverty and low-crowding areas and the disparity could not be fully explained by underlying conditions or differences in vaccine coverage (Yousey-Hindes & Hadler, 2011).

Influenza and Bacterial Pneumonia

Influenza A or B infections may result in severe illness with complications requiring medical intervention and possibly hospitalization. Complications are far more common among individuals with underlying health conditions though severe consequences from influenza infection may occur in healthy

individuals. FluSurv-NET data reveals that ~25-33% of pediatric patients admitted to a hospital with laboratory-confirmed influenza do not have any underlying comorbidities. Among adults, the proportion of observed surveillance cases that do not have an underlying condition is lower and is approximately 10%. Influenza can exacerbate currently existing conditions such as heart disease, asthma or chronic lung diseases such as COPD or emphysema.

Of specific interest in the SCD population is the potential for bacterial co-infection which is a significant cause of morbidity and mortality associated with both seasonal and pandemic influenza (Metersky, Masterton, Lode, File, & Babinchak, 2012). Additionally, children with influenza with a bacterial co-infection are more likely to have a severe illness and worse outcome (Nguyen et al., 2012; Palacios et al., 2010; Randolph et al., 2011; Williams et al., 2011). An association between influenza and *Streptococcus pneumoniae* has been understood for considerable time with influenza increasing the likelihood of development of pneumococcal meningitis (Jansen et al., 2008) and pneumonia (K. L. O'Brien et al., 2000). Examination of tissue samples from individuals who died during the 1918-1919 are consistent with secondary bacterial infection indicating it was likely secondary bacterial infections leading to the majority of deaths (Morens, Taubenberger, & Fauci, 2008).

Several mechanisms contribute to severe outcomes resulting from influenza and bacterial coinfections. Predisposition for bacterial infection by influenza may occur by enhancing bacterial adherence, disrupting respiratory epithelium or by increasing bacterial-cellular interaction (Hament, Kimpen, Fleer, & Wolfs, 1999). Influenza infection damages epithelial lung tissue (McCullers, 2006) leading to increased exposure of underlying tissue and increasing bacteremia (Florescu & Kalil, 2014; Kash et al., 2011). Typically, the course of severe illness is influenza infection followed by bacterial infection leading to severe invasive bacterial infections including pneumonia and meningitis. Studies have demonstrated the relationship is not unidirectional and bacterial infections may increase influenza activity and replication (Samji, 2009; Steinhauer, 1999; Tashiro et al., 1987). Additionally, evidence indicates a synergistic relationship between certain viral and bacterial strains where the bacteria provide an enzyme to activate hemagglutinin and in turn viral infectivity (Tashiro et al., 1987).

During the 2009 pandemic, CDC collected lung tissue specimens from fatal influenza cases. A total of 77 tissue specimens were received and analyzed for bacterial co-infections. Evidence of bacterial co-infection was present in 22 of 77 (28.5%) lung tissue specimens. Ten of the specimens were positive for *S. pneumoniae* while one was positive for *H. influenza*. Bacterial co-infections were present in a substantial number of fatal influenza infections and similar findings have been found in previous influenza pandemics (Brundage & Shanks, 2008; Morens et al., 2008).

In addition to being significant contributors to morbidity and mortality among individuals with influenza, *S. pneumoniae* and *H.influenzae* pose enhanced risk to individuals with SCD. Thus, any infection by influenza may make individuals with SCD more susceptible or vulnerable to severe bacterial co-infections. One could also presume an individual with SCD is at greater risk from *S. pneumoniae* and *H.influenzae* infections, and may in turn be more susceptible to secondary viral infections and severe influenza-related complications.

Influenza, SCD and Pneumonia

The influenza vaccine is considered the most effective means to prevent illness, hospitalization, complications and death from influenza by both CDC and WHO (CDC, 2017d; WHO, 2018). Vaccination against seasonal influenza has been shown to reduce morbidity and mortality in high--risk populations. In a seven-year study among diabetics, receipt of the seasonal influenza vaccination was associated with lower hospital admission rates due to stroke, heart failure, pneumonia or influenza and all-cause death (Vamos et al., 2016). In a study of frail elderly, a group long recommended to receive the annual vaccination, seasonal flu vaccination was associated with a 7% decrease in the risk of hospitalization and a 44% risk reduction in mortality (W. J. Lee, Chen, Tang, & Lan, 2014).

Racial disparities of influenza may partially be explained by differential vaccine update by race. For instance, it has been shown that even among cancer survivors, influenza vaccine uptake was substantially higher among white survivors than among black survivors (Stafford, Sorkin, & Steinberger,

2013). This is important since cancer survivors are at increased risk of influenza-related complications (CDC, 2016) and were a group strongly recommended for vaccination before universal influenza vaccination. Similar findings related to vaccine uptake were found among individuals with diabetes, another high-risk group for developing influenza-related complications such as hospitalization and death (Athamneh & Sansgiry, 2014).

Among elderly adults, influenza vaccine coverage was considerably different between various racial and ethnic groups; 66% coverage among whites, 50% coverage among Hispanics and only 46% among blacks based (Ompad, Galea, & Vlahov, 2006). This was before the universal recommendation for influenza vaccination. Data from the Behavioral Risk Factor Surveillance Survey (BRFSS) in 2008 yielded similar results though vaccine coverage was poor for all racial and ethnic groups under 65 years of age. In adults 50-64 years old, influenza vaccine coverage was 44.2% while it was 36.2% and 32.2 % among non-Hispanic blacks and Hispanics respectively. Among older adults 65 years or older, 72.1% of non-Hispanic whites reported receiving the influenza vaccine, 55.5% of non-Hispanic blacks and 58.7% of Hispanics reported the same (Linn et al., 2010).

According to CDC, differences in influenza immunization coverage by race and ethnicity persist. Among adults, influenza vaccine coverage was 44.5% for non-Hispanic whites, 36.6% for non-Hispanic blacks and 34.4% for Hispanics. Interestingly, among children 6 months to 17 years of age, the trend is reversed. Hispanic children have the highest vaccine coverage at 64.7% followed by non-Hispanic blacks at 60.9% and non-Hispanic whites at 55.3% (CDC, 2017e). Influenza vaccine coverage among children during the 2015-16 season was similar to the coverage in the 2014-15 season (CDC, 2017e).

Antiviral Treatment for Influenza

Patients hospitalized with severe influenza have more active and prolonged viral replication. Weakened host defenses slow viral clearance, whereas antivirals started within the first 4 days of illness enhance viral clearance (N. Lee et al., 2009). Antivirals against influenza have been on the market for

over two decades, falling into two primary drug classifications that inhibit influenza through different mechanisms. Adamantanes, including amantadine and rimantadine, operate by inhibiting the uncoating of the influenza virus inside an infected cell (Kamps & Hoffman, 2006). As of the early 2000's, adamantanes were effective against influenza A types that had been shown to previously infect humans prior to the 2009 H1N1 pandemic though they had no effect against influenza B. Adamantanes block the ion channel formed by the M2 protein of influenza A, preventing the acidification of the surrounding endocytic vesicle necessary to unpack the influenza A ribonucleoprotein particles. One of the principal downsides to adamantanes was the proclivity for influenza variants resistant to them to emerge quickly, are stable and can be transmitted as normal. In a twelve year period from 1994 to 2005, the proportion of influenza A resistant to adamantanes increased from 0.4% to 12.3% (Bright et al., 2005). By 2009, all samples tested of seasonal H3N2 and 2009 H1N1 pandemic influenza demonstrated resistance to adamantanes (Long, Sarah, Pickering & Larry, 2012). Consequently, the ACIP stopped recommending adamantanes in 2011 for treatment and chemoprophylaxis of influenza (Fiore et al., 2011).

Oseltamivir, zanamivir, peramivir, and laninamivir belong to the neuraminidase inhibitors (NAIs) family of antiviral medications. This class of drug blocks the neuraminidase enzyme of influenza preventing the budding of the viral particles out of an infected cell. Zanamivir was the first NAI developed and licensed in 1990. It was licensed for use against influenza A and B in the United States in 1999. The same year, the FDA approved the use of Oseltamivir in adults in the United States for the treatment of influenza and was later expanded to include pediatric patients. Oseltamivir has become widely prescribed and used in the United States, Europe, and Asia but not without controversy. Some studies have shown a lack of efficacy by oseltamivir in terms of reducing hospitalizations, the onset of pneumonia and other severe influenza-related outcomes. Other systemic reviews have demonstrated oseltamivir to be effective in reducing the duration of influenza symptoms by half to a full day, decrease the duration of hospitalization, and the risk of otitis media. Additionally, nausea, vomiting, headaches, kidney and psychiatric events are side effects associated with administration of oseltamivir. Therefore, some agencies have stopped recommending oseltamivir in healthy individuals as it was determined the

benefit of taking oseltamivir does not outweigh the risks of the side effects. In the United States, it is currently the most widely prescribed of the group. The biological mechanism of NAIs, distinctly different from adamantanes, allows them to be effective against both influenza A and influenza B. NAIs can be prescribed for the treatment of influenza and prophylaxis in contacts of an infected individual. In recent years there has been some debate regarding the effectiveness of antiviral medications against influenza. Peramivir is the most recently licensed NAI. It was given emergency authorization for use during the 2009 H1N1 pandemic in the United States which expired in 2010. Approval to use peramivir to treat influenza infection in adults was granted in December 2014 in the US. Laninamivir is still in clinical trials and has not been approved yet. Based on FluSurv-NET data, oseltamivir is prescribed to patients substantially more frequently than the other NAIs on the market. Resistance to NAIs was substantial in seasonal H1N1 strains tested in 2007-08 and 2008-09, 10.9% and 99.4% respectively. However, NAI resistance disappeared with the emergence of the 2009 A/H1N1 pandemic strain of influenza and has remained low since among circulating seasonal strains of influenza.

Sickle Cell Disease

Sickle cell disease, or at least the characteristic sickle-shaped erythrocytes or red blood cells, was first described in 1910 by Herrick (1910). Decades later, abnormalities in hemoglobin from sickle cells were observed (Pauling, Itano, Singer & Wells, 1949) indicating a molecular cause of the morphological changes observed in sickle cells. Further study has revealed the underlying genetic causes of SCD. SCD is actually a broad term referring to a collection of inherited, genotypes in the genes coding for the proteins that combine to form hemoglobin, the protein responsible for oxygen and carbon dioxide exchange throughout the body. These genotypes result in hemoglobin molecules capable of crystallization or polymerization which fills the erythrocyte and alters its shape into the characteristic sickle shape (Brttenham, Schecter, Noguchi, 1985).

Over a dozen sickle cell disease variations have been identified causing mild to severe disease (Rees, Williams & Gladwin, 2010). Four genotypes comprise the majority of SCD cases in the United States including HbSS, HbSC, and HbS beta 0-thalassemia and HbS beta+-thalassemia (CDC, 2017f). HbSS indicates the inheritance of the sickle cell gene from both parents and results in sickle cell anemia, the most common and severe form of SCD. HbSC occurs when one inherits the sickle cell gene from one parent and an abnormal hemoglobin "C" gene from the other parent. Normally, this is a milder form of SCD. HbS beta thalassemia occurs when one inherits the sickle cell gene from one parent and beta-thalassemia from the other, which is another form of anemia. Beta thalassemia has two forms, 0 and +. Inheriting the 0 form normally results in a severe form of SCD while the + usually yields a milder form of SCD. In the United States, the approximate proportion of each SCD is HbSS (65%), HbSC (25%), SCD-SB+-thalassemia (8%) and SCD-SB0-thalassemia (2%) (NIH, 2002).

In the United States, it is estimated between 80,000 and 100,000 individuals are living with SCD (Brousseau, Panepinto, Nimmer, Hoffman, 2010). SCD disproportionately affects the African American population in America, being present in approximately 1 in 500 African American births. By comparison, SCD is approximately present in only 1 in every 36,000 Hispanic births and 1 in 100,000 Caucasian births (Hassel, 2010).

Signs or symptoms of SCD begin to emerge in the first several months of life. Symptoms vary between individuals and may be mild to severe and may occur repeatedly throughout an individual’s life. Furthermore, since SCD is a progressive illness, symptoms and resulting outcomes typically grow in severity over time (CDC, 2017g). Symptoms of SCD include swelling in the extremities, SCD pain/SCD crisis, anemia, infection, acute chest syndrome (ACS), splenic sequestration and vision loss, leg ulcers, stroke, deep vein thrombosis and pulmonary embolism (Serjeant, 2013).

The sickle-shaped red blood cells in SCD patients do not flow through blood vessels with the same ease as blood cells in non-SCD individuals. Instead, sickle cells may bind and stick together clogging blood vessels slowing or blocking blood flow. Blocked blood vessels in the extremities may result in swelling of the hands or feet which is often one of the first signs of SCD in young children. Aside from swelling,

reduced blood flow or blocked vessels can produce mild to severe pain that may last an indeterminate amount of time.

HbSS, the most common form of SCD, is also the most severe form of SCD and often referred to as sickle cell anemia. SCD anemia occurs due to premature hemolysis of red blood cells reducing the capacity of blood to carry oxygen. Consequences of anemia are both acute and chronic. Anemia directly causes lethargy or tiredness as an individual has reduced oxygen supply which may lead to irritability, dizziness, difficulty breathing, elevated heart rate as well as slowing growth and delaying puberty (CDC, 2017g). Anemia, via red blood cell hemolysis, leads to vasculopathy, or any disease affecting the blood vessels. Common vascular complications among individuals with SCD include pulmonary hypertension and cerebral vascular accidents or stroke (Kato et al., 2006; Ohene-Frempong et al., 1998). Among individuals with SCD over ten years of age the leading causes of mortality were cerebrovascular events and trauma (Leikin et al., 1989).

Sickle Cell Disease and Bacterial Infections

Another risk inherent to individuals with SCD is increased risk of infection, particularly from encapsulated bacteria, due to functional asplenia and immature immune response systems (Wong, 2001) such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and non-Typhi *Salmonella* (Serjeant & Serjeant, 2001). Historically, the peak incidence of mortality in SCD cases occurred in children between the ages of 1 and 3 years and the principal cause was infection (Leikin et al., 1989). Routine vaccination against H. influenzae and S. pneumoniae and penicillin administration have contributed to significantly reduced morbidity (Halasa et al., 2007; Narang, Fernandez, Chin, Lerner, & Weinberg, 2012) from infection among individuals with SCD in their early years of life. Infection remains a risk to those with SCD.

Of note for this study is the relationship between influenza and secondary bacterial pneumonia often caused by the same presenting increased risk to individuals with SCD. Influenza virus infection

damages the tracheobronchial lining increasing susceptibility to bacterial invasion (Loosli, 1973). Individuals with SCD are at increased risk of infection potentially leading to fulminant sepsis from *S. pneumoniae* or *H. influenzae* (Turner et al., 1992). Therefore, in addition to vaccination against S. pneumoniae, NIH has recommended children with SCD receive annual vaccination for influenza too (NIH, 2002).

A common complication of bacterial or viral infection among individuals with SCD, though infection is not the only cause, is acute chest syndrome (ACS). ACS is defined as a new pulmonary infiltrate in a patient with SCD and fever and respiratory symptoms such as cough, shortness of breath, respiratory distress or wheezing. It is a common cause of hospitalization, potentially prolonged, and respiratory failure among those with SCD (Charache, Scott, & Charache, 1979; Vichinsky et al., 2000; Vichinsky et al., 1997). Most individuals with HbSS SCD will have at least one incidence of ACS within their first decade of life (Gill et al., 1995). Repeated episodes of ACS may indicate the development of chronic lung disease (Powars, Weidman, Odom-Maryon, Niland, & Johnson, 1988). Other causes of ACS include pulmonary fat embolization and infarction (Jain, Bakshi, & Krishnamurti, 2017). Other complications from SCD involve serious bacterial infections such as meningitis, pneumonia and osteomyelitis, stigma and dissatisfaction with their healthcare. (Jenerette & Brewer, 2010).

Sickle Cell Disease and Influenza Vaccine

The first Influenza immunogenicity study in children with sickle cell disease was reported in 1978 involving a bivalent influenza vaccine administered in two doses. The study demonstrated acceptable serum titer levels indicating acceptable response to the inoculation (Steinberg et al., 1978). A subsequent study using a single dose of trivalent influenza vaccine against influenza A(H1N1), influenza A(H3N2) and influenza B demonstrated acceptable serum antibody titer levels in 68% to 84% of school-aged recipients depending on antigen. Pre-school aged children who received two doses of the trivalent

vaccine four weeks apart were found to have lower but still acceptable titer levels (Glezen, Glezen, & Alcorn, 1983).

Low uptake rates of annual influenza vaccine were found among a population of SCD patients over the age of 16 (Gorham, Smith, Smith, Wong, & Kreze, 2015). Similar findings were demonstrated in a larger study conducted using the Wisconsin Medicaid database which demonstrated a low adherence to annual influenza vaccine recommendation at less than 22% (Beverung, Brousseau, Hoffmann, Yan, & Panepinto, 2014).

A significantly lower rate of seroconversion was observed among individuals with SCD who regularly receive blood transfusions compared to those patients who do not receive transfusions (Purohit, Alvarez, O'Brien, & Andreansky, 2012). This study also demonstrated lower immune response among children with SCD less than three years of age as seen in the general, non-SCD population.

Despite the recommendation of the influenza vaccine for those with SCD, limited information is available concerning its safety in this population. Trivalent, inactivated influenza vaccine was demonstrated to not be associated with hospitalization due to sickle cell crisis (Hambidge et al., 2012). Another study of the 2009 H1N1 vaccine among immunocompromised patients including patients with HIV, cancer and SCD determined the vaccine was well tolerated and causing no serious vaccine-related adverse events (Hakim et al., 2012). Furthermore, the 2009 H1N1 influenza vaccine demonstrated sufficient immune response in patients with SCD but reduced immunogenic response in patients with HIV or cancer.

Disparities in influenza vaccine coverage have been previously documented (Setse et al., 2011). Influenza vaccine coverage was shown to be lower among non-Hispanic black adults than among non-Hispanic white adults. Influenza vaccine coverage among non-Hispanic blacks 65 years and older was the lowest of any race/ethnicity category. Influenza vaccine coverage was lower among Hispanics than non-Hispanic whites, 18-64 years of age but similar among those 65 years and older.

Social Determinants of Vaccination in Patients with Sickle Cell Disease

Influenza disease occurrence and severity depend not only on direct biological factors but also depends on multiple social determinants which may place individuals at increased risk of exposure and development of influenza infection, decrease the likelihood for obtaining influenza vaccination and decrease access to health care. Social determinants of health include a wide array of items including access and quality of education, economic and job opportunities, access to healthcare, transportation (public or private), social support, socioeconomic conditions, residential segregation, language or literacy barriers public safety and to name a few (Secretary's Advisory Committee, 2010). SCD occurs predominantly among minorities, chiefly African Americans and to a far lesser extent, Hispanics. These are populations which have experienced prolonged socioeconomic disparity which is largely unchanged since 1980 (Stanford Center on Poverty and Inequality, 2018). Socio-economic status is a strong and consistent determinant of health outcomes worldwide (Sheiham, 2009).

It has been noted previously that influenza rates are independently associated with crowding and the proportion of poverty at the Census tract level (Yousey-Hindes & Hadler, 2011). Consistent with these findings is a study from Canada that demonstrated neighborhoods that were materially deprived utilized health care services at a higher rate than people from neighborhoods that were not materially deprived (Charland, Brownstein, Verma, Brien, & Buckeridge, 2011). Not only may living in economically depressed neighborhoods increase vulnerability to infectious diseases via induced stress (Karpati, Galea, Awerbuch, & Levins, 2002) but individuals are at increased risk of developing comorbidities such as asthma, diabetes, obesity, chronic obstructive pulmonary disorder which are development of severe influenza illness (Biggerstaff et al., 2014; Neuzil et al., 2000).

Generally speaking, positive health gradients associated with socio-economic measures across various life stages have been documented (Gray, 1982) (M. G. Marmot, Rose, Shipley, & Hamilton, 1978). Interestingly, in the United Kingdom which provides universal healthcare, health disparities between socioeconomic groups have widened over time since the inception of the National Health Service in 1948 (Gray, 1982). Additionally, a study of administrative data from Nova Scotia showed individuals

with lower SES used family physician and hospital services more than those in higher SES but used specialized services at a lower rate potentially causing disparities to widen (Veugelers & Yip, 2003). Poverty is associated with poor health outcomes (M. Marmot, 2005). Not only is this a large concern internationally since SCD is more frequent in the poorest nations (Piel, Hay, Gupta, Weatherall, & Williams, 2013) but poverty itself can result in severe consequences. For instance, prolonged poverty during childhood and its associated stress leads to reduced adult cognitive function (Evans & Schamberg, 2009). Along similar lines, SCD itself may modulate socioeconomic status. A study matching families where SCD is present to African American families without SCD demonstrated those where SCD is present had a greater frequency of single-parent and single female heads-of-household than those without SCD (Farber, Koshy, & Kinney, 1985).

Stigma Associated with Sickle Cell Disease

Unfortunately, prejudice and discrimination based upon medical conditions have a long and persistent history. Examples include leprosy, HIV/AIDS, mental illness and SCD. Stigma is defined as a mark or characteristic though typically associated with a negative connotation such as a mark of shame or discredit (Merriam-Webster, 2019). Weiss characterizes health-related stigma as "social disqualification of individuals and populations who are identified with particular health problems" (Weiss, Ramakrishna, & Somma, 2006) which is an extension of Goffman's definition of stigma, "a phenomenon where an individual is rejected due to an attribute or behavior that is deeply discredited by society" (DeFleur, 1964). Combined, the above definitions indicate individuals with chronic medical conditions such as SCD are often discredited, meaning their condition is not perceived as real or severe by those without the condition and those with the condition may face rejection even by care providers and therefore not receive the proper care required for their condition. As mentioned earlier, individuals with SCD experience greater emergency department wait times than African Americans without SCD (Haywood et al., 2013) demonstrating this point.

A recent review identified the following four important domains of stigma concerning SCD: social consequences of stigma, stigma's effect on psychological well-being, stigma's effect on physiological well-being and impact of stigma on patient-provider relationships (Bulgin, Tanabe, & Jenerette, 2018).

Social stigmatization is the process of identifying a differentiating characteristic, labeling individuals or a group by this characteristic and then separating those labeled individuals which is often coupled with devaluing the labeled group through an exercise of power (Link & Phelan, 2006). Stigmatization is common among individuals with SCD due to misunderstanding of their illness and being inextricably linked to their status as minorities (Moffitt, 2011; Telfair, Myers, & Drezner, 1998). Even in a predominantly black community where one would expect less stigmatization to occur due to race, patients with SCD still describe experiencing stigma (Anderson & Asnani, 2013).

After social stigmatization, individuals may internalize their stigmatization which can increase stress (Link & Phelan, 2006), induce feelings of shame and lead to poor outcomes (Perlick et al., 2001). Among individuals with mental health disorders, internalized stigmatization results in negative relationships for some psychosocial areas including hope, self-esteem, and empowerment (Livingston & Boyd, 2010). When interviewed, adults with SCD already indicate a propensity for feelings of inadequacy, burden upon family members, depression and suicidal ideation during sickle cell crisis (Ohaeri, Shokunbi, Akinlade, & Dare, 1995). Stigma adds to the stress already experienced by having a chronic illness and may impact adherence to treatment (Livingston & Boyd, 2010) and directly or indirectly to worse psychosocial or physiological health outcomes.

Individuals with SCD often report negative experiences towards the health care system. Such feelings and attitudes are often related to inadequate pain control during sickle cell crisis events (Bolten, Kempel-Waibel, & Pförringer, 1998; Osman et al., 2000; Strickland, Jackson, Gilead, McGuire, & Quarles, 2001). Young adults with SCD often have their credibility questioned during such encounters (Maxwell, Streetly, & Bevan, 1999) and unfortunately, the lack of perceived veracity by health care provider may impact the level of treatment provided. Additionally, when seeking care, individuals with

SCD report difficulty finding someone to discuss their concerns, fully answer their questions or address their fears and anxieties related to their illness and treatment (Lattimer et al., 2010). The lack of respect and dismissive attitude often received by individuals with SCD leads to a lack of trust in providers and the healthcare system culminating in a situation where patients then believe they may in fact be harmed by their provider (Rose, Peters, Shea, & Armstrong, 2004). Ultimately, this can lead to adult patients with SCD avoiding care altogether (Ely, Dampier, Gilday, O'Neal, & Brodecki, 2002).

Conceptual Framework

The literature review presented earlier in this chapter has highlighted the current state of research regarding influenza infections among individuals with sickle-cell disease. Limitations and gaps persist despite the research conducted to date. One of the limitations is a lack of theory-based research accounting for influenza illness and vaccine uptake within individuals with sickle cell disease. The few studies that examined influenza among those with SCD discussed earlier (Bundy et al., 2010; Inusa et al., 2010) lack theoretical frameworks to properly explain and guide further discussion as it relates to influenza among individuals with SCD. Theories are central to healthcare practice, promotion and research, (Alderson, 1998) indicating a substantial oversight in the previous SCD and influenza-related research. There are a number of reasons to construct models or theoretical frameworks including explaining observed data, guiding future data collection, identifying new questions, educating and simplifying seemingly complex interactions (J. M. Epstein, 2008).

Contracting influenza is a seemingly simple process. A person needs to be susceptible to illness, become exposed and become infected. Yet as pointed out earlier in the chapter, several factors contribute to increasing a person's susceptibility, their risk of exposure and risk of developing severe illness and the likelihood of obtaining an annual influenza vaccination, the best means of prevention against influenza. Additionally, when considering a theoretical framework to discuss influenza infection among individuals with sickle cell disease, one cannot ignore the inextricable link between race and SCD and the subsequent

health inequalities experienced by African Americans. Therefore, the conceptual model used to guide this study and presented in Figure 1 is a systems-based model that considers health inequalities arising from various social determinants. The model presented is an adaptation of a model of the social determinants of influenza illness and outbreaks as presented by (Cordoba & Aiello, 2016).

The primary strength of using a systems perspective for public health outcomes is it provides a more holistic and non-reductionist perspective (Pourbohloul & Kieny, 2011). In other words, systems thinking aims to identify and explain how things are connected within a larger entity (Peters, 2014). With this context, the model aims to explain what individual and social factors are associated with the development of influenza-related hospitalizations among individuals with SCD. A systems model also recognizes the contributing factors may change over time or new factors emerge within a changing system.

The model used to guide this study has four summary constructs representing individual factors as well as social and healthcare-related factors that influence the development of influenza illness as well as the key influenza prevention measures of annual influenza vaccination.

The first construct contains several individual attributes that may affect the likelihood of contracting influenza and developing severe influenza-related outcomes, principal among these being age and the presence of underlying medical conditions including SCD. Gender plays a role related to the hospitalization of influenza since pregnant women who test positive for influenza may be more prone to be hospitalized for influenza. Further, women tend to live longer than men and thus reach an age where they are more vulnerable to influenza infections and therefore more likely to be hospitalized or have a severe illness. Race and ethnicity are included as they are related to influenza vaccine coverage and SCD frequency is related to both race and ethnicity. An individual’s income as well as insurance coverage also contribute to likelihood of vaccine uptake, availability of healthcare and health seeking behaviors.

The second construct includes the various socioeconomic factors that influence an individual's likelihood of receiving appropriate influenza prevention factors and thus the likelihood of a severe outcome from an influenza-related illness. Income influences not only an individual's direct ability to

afford quality health care and associated prevention and intervention measures but has also been shown to be associated with a greater likelihood of influenza vaccination receipt (Linn et al., 2010). Additionally, income may dictate an individual's residence. Neighborhood characterisics such as proportion of individuals living in poverty and crowding have been shown to be independent predictors for influenza-related hospitalization (Yousey-Hindes & Hadler, 2011) and bloodstream infections (Mendu, Zager, Gibbons, & Christopher, 2012), Likewise, socioeconomic factors impact health insurance coverage and therefore have bearing upon receipt of recommended healthcare and the possibility of severe outcomes from influenza-related illness. Insurance coverage in this construct is different than at an individual level and represents availability through programs such as Medicare and Medicaid and does not reflect an individual's direct access to medical insurance via employment or adequate income. Employment opportunities within a community influence access to care by providing opportunity for work-based interventions such as immunizaiton drives but also by providing meaninful employment and income as well as employment-based insurance coverage.

The third construct relates to physician factors. Differences exist in physician availability and may vary between urban versus rural settings (Petterson, Phillips, Bazemore, & Koinis, 2013) and within urban settings. Higher physician density has been linked with lower mortality (Shi & Starfield, 2001). As discussed previously, even when physicians are available, many feel under trained to provide adequate care for individuals with SCD (Mainous et al., 2015). Physician availability and training have a direct impact on ensuring patients with SCD receive appropriate healthcare and recommendations to prevent infections such as influenza and related invasive bacterial infections.

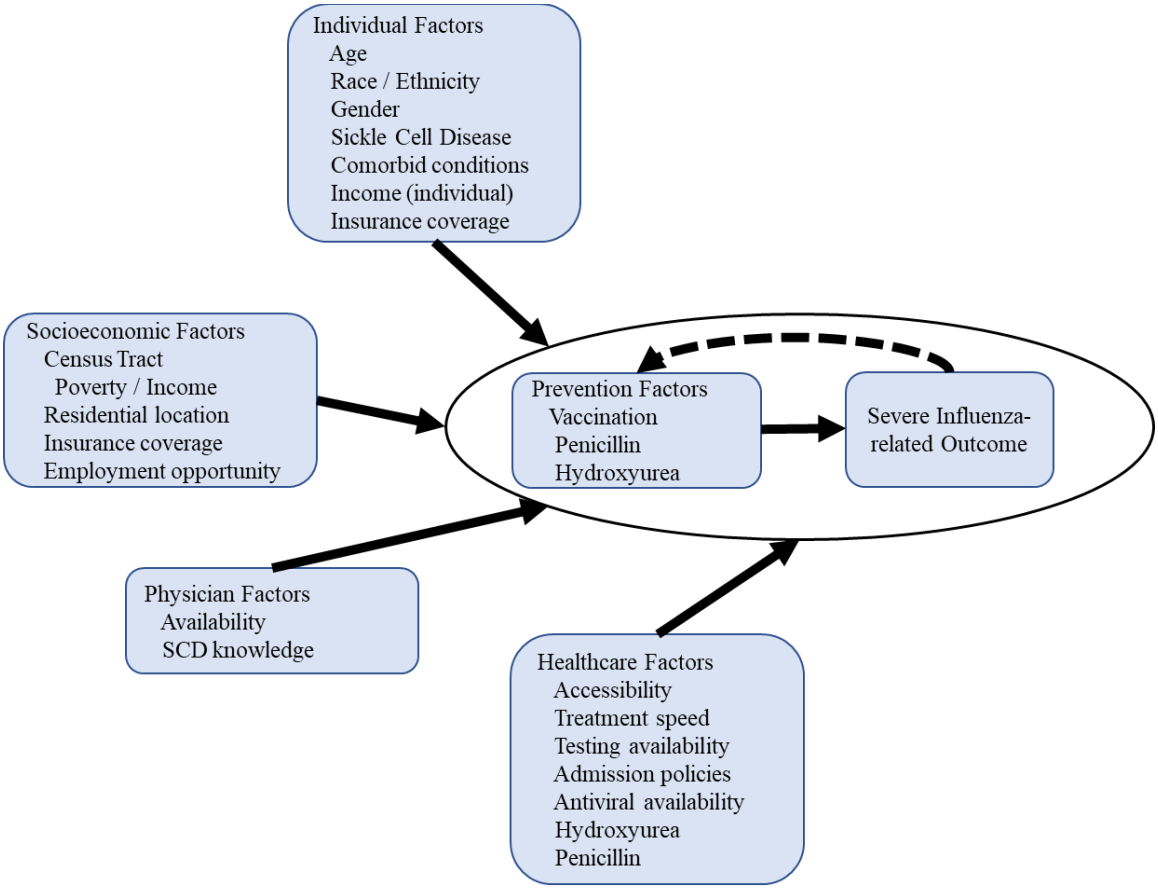
The Healthcare factors construct is a broad category that outlines items associated with prevention, and treatment of influenza-related illness for individuals with SCD. The first item, accessibility is influenced by many of the previous factors in other constructs but also has bearing on individuals receiving proper health care pre-illness for prevention measures and during illness. Tied closely with accessibility is the speed with which treatment is delivered once an individual becomes sick with influenza. Early and aggressive care for patients with SCD experiencing acute chest syndrome

reduces mortality (Jain et al., 2017). Testing availability and admission policies are both factors that are associated with healthcare and inclusion in this study. The data analyzed was derived from a surveillance system for laboratory-confirmed, hospitalized cases of influenza. Therefore, patients who were not tested, tested negative for influenza or not admitted to a hospital were not included in the dataset. From a healthcare perspective, these factors are important since acute chest syndrome is often associated with infection and identifying the etiological agent is important so correct intervention may be initiated as soon as possible such as antiviral therapy in the case of influenza infections. Admission policies may vary from one facility to another and individuals with comorbid underlying conditions such as SCD may be more prone to be admitted than patients without any underlying conditions. Hydroxyurea is the only effective treatment to prevent episodes of sickle cell crisis and regular penicillin treatment is recommended in individuals with SCD less than five years of age. Both of these treatments may have an impact on illness severity and the likelihood of hospitalization during influenza infection.

The last two constructs are related and include prevention factors and severe outcomes from an influenza-related illness. All constructs mentioned earlier feed into the possibility of each receiving influenza prevention measures such as vaccination and in the case of those with SCD, hydroxyurea, and penicillin to prevent episodes of sickle cell crisis and bacterial infections. The model also proposes that previous severe influenza infection has a feedback effect, represented by the dotted arrow, and increases the likelihood of receiving influenza vaccine and recommended preventative care for SCD.

The model presented on the next page has guided the analysis and conclusions prested in the next two chapters. Individuals with SCD face challenges particularly during care transition from pediatric coverage into adulthood where it has been found they receive less hydroxyurea, had higher SCD-related costs and more frequent SCD-related complications than pediatric patients with SCD (Blinder et al., 2013). Therefore, pediatric and adult patients will be analyzed separately. Limited studies have been conducted studying influenza in patients hospitalized with influenza. Therefore, the model provides a guide to determine where future studies should be directed to better understand the impact of influenza upon individuals with SCD.

Figure 1: Conceptual Framework



CHAPTER 3

METHODOLOGY

Research Design

A secondary data analysis was performed using data collected from the FluSurv-NET influenza surveillance system. The data analyzed were collected throughout six influenza seasons starting in the 2011-12 season through and including the 2016-17 influenza season.

Data and Methods

Data Source: Data elements used in this analysis will be derived from FluSurv-NET, a population-based influenza surveillance system previously described by Chaves et al. (2015). A standard Case Report Form was used to collect demographic and clinical information via medical chart abstraction and these data were recorded into a centralized database. FluSurv-NET conducts surveillance in thirteen states spanning 80 counties and municipalities and includes a population near 27 million people or approximately 9% of the U.S. population (Table 1).

A total of 68,470 lab-confirmed, hospitalized cases of influenza were identified in the six influenza seasons from 2011-12 through 2016-17. Influenza cases were removed before analysis for a few reasons. Firstly, Iowa and Rhode Island participated in FluSurv-NET for only one and two seasons respectively. Cases from these sites were eliminated to maintain a consistent catchment area and study population. Influenza cases where SCD status could not be determined due to incomplete or missing data were also removed. Lastly, hospital-onset influenza cases were eliminated before analysis to focus on community-onset cases of influenza resulting in hospitalizations. The remaining observations included 64,443 cases of community-onset influenza. Of these, 7,406 were among pediatric patients (<18 years of age) and 385 of these had SCD. The remaining 57,027 cases of influenza occurred among adults and 241 of these cases had documented SCD upon medical chart review.

Instrumentation: FluSurv-NET uses a standardized case report form (CRF) to collect subject information through medical chart abstraction. The study also uses a standardized form sent to a subject's primary care physician (PCP) to obtain influenza vaccine status and a telephone script used to interview subjects or a subject's proxy for the same purpose. Examples of all three forms from the 2016-17 influenza season are included in Appendices B, C, and D.

Table 1: FluSurv-NET Catchment Area and Estimated 2010 Population of each Site

State	Counties / Cities	Population (2010)
California	Alameda, Contra Costa, and San Francisco Counties	3,574,729
Colorado	Adams, Arapahoe, Denver, Douglas, and Jefferson Counties	2,636,542
Connecticut	Middlesex and New Haven	1,026,220
Georgia	Clayton, Cobb, DeKalb, Douglas, Fulton, Gwinnett, Newton, and Rockdale Counties	3,925,130
Maryland	Anne Arundel, Baltimore, Carroll, Harford, Howard Counties, and Baltimore City	2,737,070
Michigan	Lansing (Ingham, Eaton, Clinton) and Genesee Counties	883,353
Minnesota	Anoka, Carver, Dakota, Hennepin, Ramsey, Scott, and Washington Counties	2,985,405
New Mexico	Bernalillo, Chaves, Dona Ana, Grant, Luna, Santa Fe, and San Juan Counties	1,280,823
New York	Albany: Albany, Columbia, Greene, Montgomery, Rensselaer, Saratoga, Schenectady, and Schoharie; Rochester: Genesee, Livingston, Monroe, Ontario, Orleans, Wayne, and Yates Counties	NY – Albany: 1,040,035 NY – Rochester: 1,142,555
Ohio	Delaware, Fairfield, Franklin, Hocking, Licking, Madison, Morrow, Perry, Pickaway and Union Counties	1,994,536
Oregon	Clackamas, Multnomah, and Washington Counties	1,734,682
Tennessee	Cheatham, Davidson, Dickson, Robertson, Rutherford, Sumner, Williamson, and Wilson Counties	1,618,979
Utah	Salt Lake County	1,091,742

Data Collection and Procedures: Medical charts were abstracted onto the standardized CRF by trained surveillance officers at each participating study site. To ensure consistency, staff members at each site are provided training by CDC at an annual surveillance officer meeting and during regular conference calls. Information abstracted from each medical record includes patient demographics, influenza lab test results, symptoms leading to hospitalization and prior to positive influenza test, comorbid medical conditions, bacterial and viral co-infections, clinical course and interventions required such as admission to ICU, need for mechanical ventilation or Extracorporeal mechanical oxygenation (ECMO) needed, anti-viral treatment, physician clinical diagnosis, patient outcome and discharge location, ICD-9/ICD-10 discharge codes and lastly influenza vaccine status prior to admission. Influenza vaccine status is obtained in a step-wise manner until each patient's vaccine status is determined to be "Yes" with a complete date or a definitive "No." The medical chart is the first source consulted followed by a site's state vaccine registry if applicable. If vaccine status remains unknown after consulting the vaccine registry, FluSurv-NET personnel attempt to contact the patient's primary care physician (PCP). Lastly, the subject or subject's proxy is contacted and interviewed by telephone using a standardized script to obtain influenza immunization status before the individual's influenza-related hospitalization. For a patient to be considered properly immunized, they must have received a dose of influenza vaccine at least two weeks before their first positive influenza test associated with the hospitalization.

Study Population: Children (< 18 years old) and adults (≥18 years old) residing in the FluSurv-NET catchment area and hospitalized with influenza were enrolled in the FluSurv-NET surveillance study during 2011-2012, 2012-2013, 2013-2014, 2014-2015, 2015-16 and 2016-17 influenza seasons. For this study, the influenza season is defined as admission to a hospital on or between October 1st and April 30th of each respective season.

FluSurv-NET: Starting in 2003-04, CDC, in cooperation with state health departments and academic partners has been conducting active, population-based surveillance for cases of laboratory-

confirmed, hospitalized influenza under the Influenza-Associated Hospitalizations Surveillance program (FluSurv-NET) program. FluSurv-NET conducted surveillance for pediatric influenza cases for two years and expanded surveillance to include all ages beginning in 2005-06. FluSurv-NET currently operates in thirteen states, includes 80 counties and municipalities covering a population of approximately 27 million people or roughly 9% of the US population. Surveillance data collected includes demographic data for each patient, symptoms at case presentation, comorbid conditions including sickle cell disease, bacterial and viral co-detections, clinical course and outcome. Influenza vaccination status and antiviral treatment for each case are also collected (Chaves et al., 2015). Data is collected by trained surveillance officers using a standardized data collection tool.

Cases are defined as individuals who tested positive for influenza and were admitted to a hospital for any amount of time within fourteen days of the positive test or were hospitalized at the time of their first positive influenza test. Acceptable tests include rapid influenza diagnostic tests, reverse transcriptase-polymerase chain reaction (RT-PCR), serology, DFA, IFA, rapid molecular tests, and viral culture. Admission to a hospital is defined as admission to a hospital floor or ward for any amount of time or admission to observation given the patient spent a combined time of 24 hours or more in the emergency department and observation ward.

Case data were collected by chart abstraction using a standardized case report form (see attached). Information collected for FluSurv-NET includes patient demographics, influenza test information, symptoms before hospitalization, underlying comorbidities, ICU admission and duration, medical interventions including ventilation and antiviral medication use, bacterial and viral co-infections, x-ray results, discharge diagnosis, ICD9/ICD10 discharge codes, outcome, and influenza vaccination status before hospitalization. If vaccination status is incomplete or unknown following medical chart abstraction, additional steps are taken to obtain complete information which includes the full date a case received vaccine or confirmation that the case did not receive a vaccine for the current season. Following chart abstraction each site would consult their state vaccine registry if appropriate, then contact a case's primary care physician or care provider (i.e. nursing home) and lastly FluSurv-NET will contact the

patient, parent in the case of a pediatric case or a case's proxy who can answer on the case's behalf in the event of death, disability or inability to provide adequate medical history.

Definitions:

1. Patients will be considered to have been positive for a respiratory symptom if the patient experienced any of the following symptoms or the symptoms were present upon medical exam in the two weeks prior to a positive flu test: nasal congestion, runny nose, cough, sore throat, shortness of breath or were characterized upon medical exam as having respiratory distress, upper respiratory illness, influenza-like illness or wheezing.
2. Adult patients were categorized as obese if there they had a reported Body Mass Index (BMI) score of ≥30.0 or if either obesity or morbid obesity was noted in the medical chart if a BMI score was not available and could not be calculated from height and weight. Pregnant women are excluded from obesity determination.
3. Patients were assigned asthma as an underlying condition if asthma or reactive airways disease were noted in the medical record.
4. Patients were considered to have chronic lung disease if cystic fibrosis, emphysema, COPD or another unspecified chronic lung disorder was present in a patient's medical history.
5. Patients were considered positive for diabetes if Type 1 or Type 2 diabetes was present in their medical history.
6. Patients assigned to the sickle cell disease group were identified to have sickle cell disease and not only sickle cell trait.
7. Cardiovascular disease group includes patients with one or more of several underlying conditions including atherosclerotic cardiovascular disease, atrial fibrillation, cerebral vascular accident/stroke, a congenital heart condition, coronary heart disease, heart failure/CHF or another unspecified cardiovascular condition.
8. Patients were considered to have an underlying neuromuscular disorder if one or more of the following were identified during medical chart abstraction in the patient's history; Duchenne

muscular dystrophy, muscular dystrophy, multiple sclerosis, mitochondrial disorder, myasthenia gravis or another unspecified neuromuscular condition.

9. Patients were considered to have a neurologic disorder if cerebral palsy, cognitive dysfunction, dementia, developmental delay, Down syndrome, plegia/paralysis, seizure/seizure disorder or neurologic conditions were noted in the medical chart.
10. Patients were considered to be immunocompromised if one or more of the following conditions were listed in their medical history; HIV, AIDS, cancer (current or in treatment in past 12 months), complement deficiency, immunoglobulin deficiency, immunosuppressive therapy, organ transplant, stem cell transplant, steroid therapy within 2 weeks of hospital admission or another unspecified immunocompromising condition.
11. Patients were classified as having a renal disease if they had chronic kidney disease including chronic renal insufficiency, end-stage renal disease, required dialysis, glomerulonephritis, nephrotic syndrome or another unspecified chronic renal disorder.

Measures

The dependent variables of this study are the measures to determine whether individuals with SCD hospitalized due to influenza have increased the risk of severe outcomes compared to individuals hospitalized with influenza without SCD. The variables include admission to an ICU and diagnosis of pneumonia at discharge.

Dependent Variables

1. Clinical interventions
    a. Admission to ICU (0 = No, 1 = Yes)
2. Patient Outcomes
    a. Diagnosis of pneumonia at discharge (0 = No, 1 = Yes)

Independent Variables

1. Sickle Cell Disease

    0 = No

    1 = Yes

2. Gender

    0 = Female

    1 = Male

3. Race

    1 = White, Non-Hispanic

    2 = Black, Non-Hispanic

    3 = Other

    4 = Unknown

4. Ethnicity

    0 = Non-Hispanic

    1 = Hispanic

    2 = Unknown

5. Age (Continuous)

6. Influenza immunization received

    0 = No

    1 = Yes

7. Received antiviral treatment

    0 = No

    1 = Yes

8. Chronic medical condition

    0 = No

    1 = Yes

Data Analysis

Data were analyzed using SAS version 9.4 using Survey and Survey Logistic procedures. The analysis was performed using a complex sample analysis. FluSurv-NET study states were considered strata in the analysis, individual counties were treated as clusters and the sub-groups of interest for comparison were analyzed as domains. Individual subjects were given appropriate weights based on county of residence. Pediatric cases (<18 years) and adults (≥18 years) were analyzed separately. Analysis began with a description of the demographic characteristics of the patients identified in the surveillance system by SCD status. Missing data for influenza vaccine status, diagnosis of pneumonia and mechanical ventilation were imputed using Hot Deck imputation. Imputation cells were created using gender and age groups (0 – 5 months, 6 months – 17 years, 18 – 49 years, 50 – 64 years and 65 years of age and older). Logistic regression was used to estimate the risk of severe outcomes, ICU admission or diagnosis of pneumonia, during influenza-related hospitalization related to SCD. Age, race and ethnicity, gender, influenza immunization status, antiviral medication receipt and presence of any other chronic medical condition were included as confounders in logistic regression models.

Summary of the Study Methodology

A majority of SCD patients were identified from a subset of EIP study sites. EIP sites were selected to represent the U.S. population but differences exist between sites. Observed differences in SCD rates among hospitalized influenza cases may be due to population differences or may represent differences in hospitalization practices between EIP study sites or specific healthcare facilities. Sub-analysis from sites with sufficient representation of SCD should be considered to determine if observed results remain. FluSurv-NET focuses on laboratory-confirmed, hospitalized cases of influenza which eliminates the possibility of comparing hospitalized cases against non-hospitalized cases. A smaller, targeted study comparing hospitalized and non-hospitalized cases of influenza cases with SCD may

provide additional insight regarding hospitalization practices of SCD patients and the impact of influenza among the SCD population.

CHAPTER 4

RESULTS

Descriptive Statistics

The results presented in this chapter are based on data from the FluSurv-NET surveillance system, a surveillance system which captures hospitalized cases of laboratory-confirmed influenza spanning six influenza seasons, 2011-12 through 2016-17. Following removal of hospital-onset cases, cases from temporary FluSurv-NET study sites and cases with indeterminate sickle cell disease status, 64,433 cases of laboratory-confirmed, hospitalized cases remained. Of the 64,433 cases, 7,406 were pediatric cases under 18 years of age and 57,027 were adult cases.

The proportion of SCD as an underlying condition among patients hospitalized with influenza varied by age and by study site. These results are summarized in Tables 2 and 3. Of the 7,406 pediatric cases of laboratory-confirmed, hospitalized cases of influenza, 391 (5.3%) had documented SCD. In the adult population, 241 of 57,027 (0.42%) patients hospitalized due to influenza had documented SCD upon medical chart abstractions representing a considerably smaller proportion than among the pediatric population. Influenza tends to affect the age extremes while individuals with SCD have a shorter life expectancy than those who do not. Table 3 summarizes the frequency of SCD as a comorbid condition among cases of all ages and adults aged 18-49 years old. The 18-49 age group includes 11,084 laboratory-confirmed, hospitalized cases of influenza of the 57,027 among all adults. Despite representing only 19.4% of influenza cases among adults, 202 of 241 or 83.8% of adult individuals with SCD were observed in this age group.

The proportion of influenza cases with documented SCD as an underlying comorbid condition varied by FluSurv-NET site. This is not surprising since the racial population distribution differs substantially. Among the pediatric population, the proportion of hospitalized influenza cases with SCD ranged from 0.24% in New Mexico to 12.1% in Georgia. In the adult population, the smallest observed proportion was in Utah (0.09%) and the Georgia site reported the largest proportion of 0.89%. Among

adults 18-49 years, the proportion of influenza cases with reported SCD ranges from 0.09% in Utah to 0.89 in Georgia. Among cases of all ages, Georgia had the greatest proportion of influenza cases with SCD at 2.9% while New Mexico had the lowest at 0.14%.

Table 4 presents the frequency of laboratory-confirmed, hospitalized cases of influenza and proportion of sickle cell disease by gender and age group. Overall, there was a greater proportion of females hospitalized with laboratory-confirmed influenza than males (54.0% female vs. 46.0% male). The proportion of SCD among cases of all ages was 1.0% among female and male patients admitted due to influenza. Males account for 54.9% of pediatric influenza cases and SCD was reported in 5.0% of these patients while SCD was observed in 5.6% of the female pediatric patients. Females make up 55.4% of adult influenza cases and SCD was identified in 0.48% of adult females admitted with influenza and in 0.35% of adult male patients.

Table 5 presents the frequency and proportion of influenza cases as well as SCD by age category. In the <6 months of age category there were 1,189 cases of influenza representing 1.8% of total observed influenza cases. Nineteen of these cases had SCD or 1.6%. In the next age category including patients aged 6 months to 17 years of age, there were 6,230 hospitalized cases of influenza observed. Of these, 372 or 6.0% were determined to have SCD. There were 11,083 cases of influenza observed among young adults ranging in age from 18 – 49 years of age. In this group, 202 cases or 1.8%, were determined to have SCD. The 50 – 64 year age group included 13,336 cases of hospitalized influenza. Among this group, 25 cases or 0.2% reported having SCD. The 65 and over age category accounted for 32,595 cases of hospitalized influenza or more than 50% of all observed influenza cases. Fourteen, or 0.04%, of these cases had SCD.

Influenza Prevention, Intervention and Outcome Estimates

Table 6 summarizes estimated frequencies of influenza prevention, intervention, complications and outcomes of patients by SCD status and patient age category; pediatric <18 years of age and adults 18

years and older. Among pediatric patients hospitalized with laboratory-confirmed influenza, patients with SCD had a higher estimated proportion of receiving annual influenza immunization before hospitalization (Mean 0.55, CI 0.51 to 0.59) compared to pediatric patients hospitalized with influenza without SCD (Mean 0.40, CI, 0.38 to 0.42). Pediatric patients hospitalized due to influenza who were positive for SCD also received antiviral medications more frequently than those without SCD, (Mean 0.841, CI, 0.79 to 0.89) vs. (Mean 0.74, CI, 0.70 to 0.77). The proportion of patients who had bacterial infections was greater among pediatric patients hospitalized with influenza without SCD (Mean 0.019, CI, 0.013 to 0.025) than pediatric patients with SCD (Mean 0.005, CI 0.000 to 0.010). Similarly, the estimated proportion of patients diagnosed with pneumonia was higher among pediatric patients hospitalized with influenza without SCD (Mean 0.174, CI, 0.156 to 0.193) than among similar patients with SCD (Mean 0.061, CI, 0.035 to 0.088). The proportion of pediatric patients without SCD admitted to an ICU (Mean 0.200, CI, 0.179 to 0.222) was greater than the proportion observed among pediatric patients with SCD who were admitted with influenza (Mean 0.051, CI, 0.021 to 0.080). The proportion of pediatric patients admitted with influenza without SCD who required mechanical ventilation was (Mean 0.056, CI, 0.046 to 0.066) which was greater than the proportion observed among pediatric patients with SCD (Mean 0.006, CI, -0.001 to 0.014). Among pediatric patients hospitalized due to influenza who did not have SCD, the proportion who died was (Mean 0.010, CI, 0.006 to 0.015) and no deaths were observed among pediatric patients with SCD, (Mean 0.000, CI, 0.000 to 0.000).

Among adult patients hospitalized with influenza, those with SCD had a lower proportion of who received the influenza vaccine before hospitalization than adults who do not have SCD (Mean 0.442, CI, 0.380 to 0.504) compared to (Mean 0.540, CI, 0.529 to 0.551). There was no observable difference in the proportion of adult patients admitted with influenza who received antiviral medication due to SCD status; (Mean 0.844, CI, 0.829 to 0.859) among those without SCD and (Mean 0.880, CI, 0.808 to 0.953) among adult patient with SCD. The proportion of adult patients admitted with influenza who also experienced a secondary bacterial infection was higher among patients without SCD (Mean 0.036, CI, 0.031 to 0.041) compared to those with SCD (Mean 0.014, CI, -0.001 to 0.028). Similarly, the proportion of adult patients

hospitalized due to influenza who were diagnosed with pneumonia was higher among those without SCD (Mean 0.231, CI, 0.222 to 0.241) than among those with SCD (Mean 0.117, CI, 0.053 to 0.182). The proportion of adult patients admitted to a hospital with influenza that required admission to an ICU was higher among patients without SCD (Mean 0.182, CI, 0.171 to 0.193) than among patients with SCD (Mean 0.088, CI, 0.048 to 0.128). Among adults hospitalized with laboratory-confirmed influenza, the estimated proportion of patients that required mechanical ventilation was greater among those without SCD (Mean 0.078, CI, 0.072 to, 0.084) than among those with SCD (Mean 0.013, CI, -0.004 to 0.030). Lastly, the proportion of adult patients admitted with influenza who died during hospitalization was greater in patients without SCD (Mean 0.038, CI, 0.034 to 0.042) than in patients with SCD (Mean 0.002; CI, -0.002 to 0.005).

Table 7 presents the results from a parallel analysis as presented in Table 6 restricting the analysis to African American patients. Among pediatric, African American patients admitted to a hospital due to influenza who had SCD, the estimated proportion who received an annual influenza vaccine was (Mean 0.631, CI, 0.533 to 0.730) and was greater than among similar patients without SCD (Mean 0.374, CI, 0.297 to 0.451). There was no observable difference in the proportion of pediatric, African American patients administered antiviral medications based upon SCD status; (Mean 0.783, CI, 0.734 to 0.832) in those without SCD and (Mean 0.840, CI, 0.763 to 0.917). There was no observable difference in the proportion of pediatric, African American patients who developed secondary bacterial infections based on SCD status; (Mean 0.020, CI, 0.008 to 0.031) in those without SCD and (Mean 0.009, CI, -0.004 to 0.022). The proportion of pediatric, African American patients admitted with influenza and diagnosed with pneumonia was greater among those without SCD (Mean 0.219, CI, 0.159 to 0.280) than those with SCD (Mean 0.069, CI, 0.006 to 0.117). The proportion of pediatric, African American patients hospitalized with influenza that required ICU admission was greater among those without SCD (Mean 0.171, CI, 0.125 to 0.217) than among those with SCD (Mean 0.062, CI, 0.006 to 0.117). Among pediatric, African American patients admitted to a hospital with influenza, the proportion that required mechanical ventilation was higher among those without SCD (Mean 0.055, CI, 0.033 to 0.076) compared

to those with SCD (Mean 0.016, CI, 0.001 to 0.030). The proportion of pediatric, African American patients admitted due to influenza who experienced death was also greater among those without SCD (Mean 0.012, CI, 0.001 to 0.023) than those who did have SCD (Mean 0.000, CI, 0.000 to 0.000) where no deaths were observed.

Among adult, African American patients admitted to a hospital with influenza, there was no observable difference in the proportion who received an annual influenza vaccine based on SCD status; (Mean 0.542, CI, 0.504 to 0.580) among those without SCD and Mean (0.476, CI, 0.339 to 0.613) among those with SCD. In this same population, there was no difference observed in the proportion of patients who received antiviral medications during hospitalization dependent on SCD status; (Mean 0.831, CI, 0.802 to, 0.860) in those without SCD and (Mean 0.860, CI 0.835 to 0.969) among those with SCD. Among adult, African American patients hospitalized due to influenza, the proportion that developed a bacterial infection was higher among patients without SCD (Mean 0.040, CI 0.028 to 0.052) than among those with SCD (0.004, 95% CI, -0.001 to 0.013). Likewise, the proportion of adult African American patients admitted with influenza that did not have SCD and were diagnosed with pneumonia (Mean 0.236, CI, 0.214 to 0.258) was greater than among adult, African American patients without SCD (Mean 0.09, CI 0.016 to 0.182). The need for mechanical ventilation intervention was observed more frequently among adult, African American patients admitted to a hospital with influenza without SCD (Mean 0.091, CI, 0.074 to 0.107) than among similar patients with SCD (Mean 0.020, CI -0.009 to 0.049). Lastly, the proportion of adult, African American patients who died was greater among those without SCD (Mean 0.041, CI, 0.033 to 0.050) than among those with SCD (Mean 0.003, CI, -0.003 to 0.008).

Logistic Regression, All Races

Logistic regression was performed to assess the effect of SCD on the development of pneumonia and ICU admission while controlling for gender, age, race, and ethnicity, receipt of annual influenza vaccine and administration of antiviral medication during influenza-related hospital admissions. A total of

eight logistic regression models were constructed to examine the effect of SCD on ICU admission and the development of pneumonia in pediatric and adult patients separately. The second set of logistic regression models were evaluated looking at the same outcomes in the same age groups limited to African American patients only. The data for the eight models are summarized in Table 8 through Table 11.

Table 8 summarizes two logistic models to evaluate the effect of SCD on ICU admission among pediatric and adult patients separately. Gender, age, race and ethnicity, receipt of influenza vaccine, treatment with antiviral medication and presence of underlying medical conditions were also included in the model. Among pediatric patients admitted to a hospital with laboratory-confirmed influenza, those with SCD had significantly lower odds for admission to an ICU than those without SCD (AOR 0.120, CI, 0.061 to 0.226). Gender had no noticeable effect on admission to an ICU among pediatric patients admitted due to influenza. Age had a positive association with the risk of admission to an ICU among pediatric patients admitted to a hospital with influenza (5-year AOR 1.240, CI, 1.093 to 1.409). Pediatric, African American patients admitted with influenza had significantly higher odds of ICU admission (AOR 1.491, CI, 1.115 to 1.995) compared to pediatric, white patients admitted to a hospital with influenza. Pediatric patients hospitalized with influenza of other race categories did not have a noticeable effect on the odds of ICU admission (AOR 0.862, CI, 0.578 to 1.288) compared to pediatric, Caucasian patients. Similarly, pediatric patients admitted to a hospital due to influenza of unknown race did not have a noticeable effect on the odds of ICU admission (AOR 0.973, CI, 0.704 to 1.345) compared to pediatric, white patients. Among pediatric patients hospitalized with influenza, Hispanic ethnicity had no observable effect on the odds of ICU admission (AOR, 0.861, CI, 0.575 to 1.288) compared to non-Hispanic, pediatric patients admitted to a hospital with influenza. Among pediatric patients hospitalized with influenza, those of unknown Hispanic ethnicity, there was no noticeable effect on the odds of admission (AOR 1.004, CI 0.751 to 1.343) to an ICU during their hospitalization compared to non-Hispanic pediatric patients. Among pediatric patients, receipt of an annual influenza immunization had no noticeable effect on the odds of ICU admission (AOR 1.003, CI, 0.853 to 1.180) compared to those who did not receive an annual influenza vaccine before hospital admission. Receipt of antiviral medication in

pediatric patients admitted with laboratory-confirmed influenza was associated with increased odds of ICU admission (AOR 2.089, CI 1.536 to 2.842) compared to pediatric patients who were not administered antiviral medications. In pediatric patients admitted to a hospital with influenza, the presence of an underlying, chronic medical condition had no noticeable impact on the odds of admission to an ICU (AOR 1.198, CI 0.978 to 1.467) compared to pediatric patients without an underlying, chronic medical condition.

In adult patients hospitalized with laboratory-confirmed influenza, those with SCD had lower odds of requiring ICU admission (AOR 0.236, CI 0.159 to 0.351) during their hospitalization than adult patients who did not have SCD. Adult males hospitalized with influenza had increased odds of admission to an ICU (AOR 1.172, CI 1.087 to 1.264) compared to adult females admitted with influenza. Age, among adult patients hospitalized with influenza, had a negative association with the risk of admission to an ICU (5-year AOR 0.966, CI 0.956 to 0.975). In adults admitted to a hospital due to influenza, there was no noticeable effect on the odds of admission to an ICU among African Americans (AOR 0.908, CI 0.802 to 1.027) or those of other races (AOR 0.901, CI 0.776 to 1.046) compared to those of Caucasian race. Adults of unknown race had lower odds of admission to an ICU (AOR 0.781, CI 0.640 to 0.953) during their influenza-related hospitalization compared to Caucasian adults hospitalized with influenza. Hispanic ethnicity had no noticeable effect on the odds of ICU admission (AOR 1.181, CI, 0.856 to 1.629) compared to those of non-Hispanic ethnicity among adults hospitalized due to influenza. Similarly, those of unknown ethnicity also had no noticeable effect on the odds of ICU admission (AOR 1.063, CI 0.924 to 1.209) compared to other adults admitted with influenza who were not of Hispanic ethnicity. Among adults who were hospitalized with laboratory-confirmed influenza, receipt of an annual influenza vaccine was associated with lower odds of admission to an ICU (AOR 0.871, CI 0.814 to 0.932) compared to those who did not receive an annual influenza vaccine. Adults hospitalized with influenza who received antiviral medications had increased odds of ICU admission (AOR 1.469, CI, 1.255 to 1.720) compared to adults who did not receive antiviral medications. Adults hospitalized with influenza

who had chronic, underlying medical conditions had higher odds of ICU admission (AOR 1.675, CI 1.364 to 2.056) compared to adults hospitalized with influenza without any underlying medical conditions.

Table 9 presents the results of a logistic regression model to evaluate the effect of SCD on the development of pneumonia during influenza-related hospitalizations in pediatric and adult patients. Gender, age, race and ethnicity, receipt of influenza vaccine, treatment with antiviral medication and presence of underlying medical conditions were also included in the model. Pediatric patients hospitalized with laboratory-confirmed influenza who had SCD had lower odds (AOR 0.233, CI, 0.129 to 0.420) of diagnosis of pneumonia before hospital discharge than pediatric patients without SCD. In pediatric patients, the male gender did not have a noticeable effect on the odds of a diagnosis of pneumonia (AOR 0.780, CI 0.601 to 1.013) compared to pediatric patients who were female. In pediatric patients admitted to a hospital with influenza, age had no association with the risk of diagnosis of pneumonia (5-year AOR 0.961, CI 0.858 to 1.104). Among pediatric patients, those of African American race had no noticeable difference in the odds of pneumonia diagnosis (AOR 1.342, CI 0.993 to 1.813) during influenza-related hospitalization compared to Caucasian pediatric patients. Pediatric patients in the other race category had no noticeable effect on the odds of pneumonia development among pediatric patients hospitalized with influenza (AOR 1.214, CI, 0.756 to 1.950) compared to white pediatric patients. Pediatric patients of unknown race have no noticeable difference in the odds of pneumonia diagnosis (AOR 0.662, CI 0.436 to 1.005) compared to pediatric Caucasian patients. Pediatric, Hispanic patients admitted to a hospital due to influenza did not have noticeably different odds of pneumonia diagnosis (AOR 1.624, CI 0.905 to 2.916) during hospitalization compared to pediatric patients who were not Hispanic. Similarly, pediatric patients of unknown ethnicity hospitalized with influenza did not have odds that were noticeably different from pediatric patients who were not of Hispanic ethnicity (AOR 0.940, CI 0.687 to 1.287) for the diagnosis of pneumonia during hospitalization. Receipt of the annual influenza immunization did not have a noticeable effect on the odds of pneumonia diagnosis (AOR 1.028, CI 0.869 to 1.216) compared to those who did not receive the vaccine. Pediatric patients admitted for influenza who received antiviral medications had a higher odds for pneumonia diagnosis (AOR 1.773, CI 1.377 to 2.284) compared to those who did not

receive antiviral medications during hospitalization. Pediatric patients with chronic medical conditions did not have increased odds for the development of pneumonia (AOR 0.855, CI 0.689 to 1.061) during influenza-related hospitalizations compared to pediatric patients without chronic medical conditions.

Adult patients hospitalized with lab-confirmed influenza who had SCD had lower odds (AOR 0.407, CI, 0.255 to 0.648) with SCD diagnosis of pneumonia before hospital discharge than adult patients without SCD. Male adults had greater odds for the development of pneumonia during influenza-related hospitalizations than females (AOR 1.221, CI, 1.121 to 1.331). Age, among adult patients, had a positive association with the risk for the diagnosis of pneumonia during influenza-related hospitalization (5-year AOR 1.015, CI, 1.005 to 1.025). African American adult patients did not have significantly different odds than Caucasian patients for the development of pneumonia (AOR 0.882, CI, 0.774 to 1.005), while patients of other races had increased odds for pneumonia diagnosis (AOR 1.207, CI, 1.015 and 1.435) compared to Caucasian adults. Adult patients hospitalized due to influenza with unknown race had lower odds (AOR 0.812, CI, 0.703 to 0.938) for the development of pneumonia compared to adult Caucasians hospitalized with influenza. Hispanic adult patients had increased odds for the diagnosis of pneumonia (AOR 1.357, CI, 1.134 to 1.624) during influenza-related hospitalization compared to non-Hispanic patients. Adult patients of unknown ethnicity had no noticeable difference in their odds of pneumonia diagnosis (AOR 1.001, CI 0.896 to 1.118) compared to non-Hispanic adults. Receipt of influenza vaccination before hospital admission was associated with a lower odds of pneumonia diagnosis (AOR 0.913, CI 0.862 to 0.968) compared to those who did not receive an annual influenza vaccine among adults hospitalized due to influenza. Receipt of antiviral medication during an influenza-related hospitalization increased the odds for the development of pneumonia (AOR 1.202, CI, 1.075 to 1.345) compared to those who did not receive antiviral medications among adult patients. The presence of chronic medical conditions did not have a noticeable effect on the odds of pneumonia diagnosis (AOR 0.838, CI 0.683 to 1.030) compared to those without chronic medical conditions among adults admitted to a hospital with influenza.

Logistic Regression, African American Patients

Logistic regression models were produced to examine the effect of SCD upon the odds of ICU admission and pneumonia diagnosis among pediatric and adult African American patients. These models are presented in Tables 10 and 11. Gender, age, ethnicity, receipt of influenza vaccine, treatment with antiviral medication and presence of underlying medical conditions were also included in the models. Among pediatric, African American patients hospitalized with influenza, those with SCD had lower odds of admission to an ICU (AOR 0.066, CI, 0.012 to 0.349) compared to pediatric, African American patients that did not have SCD. Pediatric, African Americans males hospitalized with influenza had higher odds of ICU admission compared to pediatric, African American female patients (AOR 2.441, CI, 1.078 to 5.525). Age had no noticeable association on the risk of ICU admission among pediatric, African American patients admitted to a hospital due to influenza infection (5-year AOR 1.409, CI, 0.778 to 2.551). Pediatric, African American patients of Hispanic ethnicity did not have odds for ICU admission that was noticeably different from that of pediatric, African American patients who were non-Hispanic (AOR 0.312, CI, 0.067 to 1.454). Pediatric, African American patients with unknown ethnicity had lower odds for ICU admission (AOR 0.159, CI 0.044 to 0.576) compared to pediatric, African American patients who were non-Hispanic. Among pediatric, African American patients hospitalized due to influenza, receipt of annual influenza vaccine had no noticeable impact on the odds of ICU admission (AOR 2.192, CI 0.893 to 5.384) compared to similar patients who did not receive an annual influenza vaccine. Administration of antiviral medication among pediatric, African American patients admitted to a hospital due to influenza had no noticeable effect on the odds of ICU admission (AOR 2.009, CI 0.571 to 7.066) versus those that did not receive antiviral medications. In pediatric, African American patients admitted to a hospital with laboratory-confirmed influenza, the presence of a chronic medical condition increased the odds of ICU admission (AOR 2.510, CI 1.238 to 5.090) compared to similar patients that did not have an underlying chronic medical condition.

Among adult, African American patients admitted to a hospital due to an influenza-related illness, those with SCD had lower odds of ICU admission (AOR 0.167, CI, 0.058 to 0.480) compared to those

without SCD. In this group of patients, being male increased the odds of ICU admission (AOR, 2.095, CI, 1.199 to 3.662) compared to adult female, African American patients. Among adult, African American patients, age was negatively associated with the risk of ICU admission (5-year AOR 0.909, CI, 0.850 to 0.970) during influenza-related hospitalization. Adult, African American patients of Hispanic ethnicity did not have a noticeable difference in odds for ICU admission (AOR 1.575, CI 0.227 to 10.94) compared to non-Hispanic, adult African American patients. Likewise, adult, African American patients of unknown ethnicity did not have noticeably different odds of ICU admission (AOR 0.550, CI 0.295 to 1.022) compared to non-Hispanic, African American adults admitted to a hospital with influenza. Receipt of annual influenza vaccine in adults, African American patients hospitalized with influenza did not have a noticeable effect on the odds of ICU admission (AOR 1.276, CI 0.772 to 2.108) compared to those who did not receive influenza vaccine. Treatment with antiviral medication during influenza illness among adult, African American patients admitted to a hospital with influenza had higher odds (AOR 2.384, CI, 1.312 to 4.330) compared to those who did not receive antiviral medication. The presence of a chronic medical condition increased the odds of ICU admission (AOR 2.122, CI 1.028 to 4.380) among adult, African American patients hospitalized with influenza compared to those without any chronic medical conditions.

Table 11 summarizes the final two logistic regression models to evaluate the impact of SCD on the diagnosis of pneumonia among African American patients hospitalized with influenza. Two models are presented, one for pediatric patients and one for adult patients. Both models also include age, gender, ethnicity, influenza vaccine status, treatment with antiviral medication and presence of any underlying medical condition.

Among pediatric, African American patients hospitalized with laboratory-confirmed influenza, those with SCD had lower odds for the diagnosis of pneumonia (AOR 0.052, CI, 0.012 to 0.217) than similar patients without SCD. In this group, being male had no noticeable effect on the odds of pneumonia diagnosis (AOR 1.169, CI 0.323 to 4.238) compared to African American pediatric female patients. Age had no noticeable association with the risk of pneumonia diagnosis (5-year AOR 1.700, CI

0.828 to 3.480) among African American pediatric patients admitted due to influenza. African American, pediatric patients of Hispanic ethnicity had lower odds for the diagnosis of pneumonia (AOR 0.122, CI 0.025 to 0.591) during influenza-related hospitalization than pediatric, African American patients who are non-Hispanic. Pediatric, African American patients with unknown ethnicity had no noticeable difference in odds of pneumonia diagnosis (AOR 0.503, CI 0.185 to 1.364) compared to pediatric, African American patients of non-Hispanic ethnicity. Receipt of influenza vaccine among pediatric, African American patients hospitalized with influenza did not have noticeably different odds (AOR 2.210, CI 0.877 to 5.564) from pediatric, African American patients who did not receive an influenza vaccine. Administration of antiviral medications among pediatric, African American patients admitted to a hospital with influenza had increased odds (AOR 4.312, CI 1.694 to 10.98) compared to similar patients who were not administered antiviral medications. The presence of chronic medical conditions among pediatric, African American patients hospitalized with influenza did not have a noticeable effect on the odds of pneumonia diagnosis (AOR 1.056, CI 0.399 to 2.793) compared to pediatric, African American patients without chronic medical conditions.

Among adult, African American patients admitted to a hospital with laboratory-confirmed influenza, those who had SCD had lower odds for the development of pneumonia during their hospitalization compared to African American adults without SCD (AOR 0.205, CI, 0.067 to 0.630). Adult, African American males hospitalized with influenza did not have an odds for the diagnosis of pneumonia (AOR 1.393, CI 0.761 to 2.550) that was noticeably different from that in adult, African American females. Age had no noticeable association on the risk of pneumonia diagnosis among adults, African Americans admitted with influenza (5-year AOR 0.941, CI 0.859 to 1.030). Hispanic, African American adults hospitalized with influenza had lower odds of pneumonia diagnosis (AOR 0.300, CI 0.107 to 0.837) than non-Hispanic, African American adults hospitalized with influenza. Likewise, African American adults admitted with influenza of unknown ethnicity had lower odds for the diagnosis of pneumonia (AOR 0.496, CI 0.303 to 0.810) compared to non-Hispanic, African American adults. In adult, African American patients hospitalized with influenza, receipt of influenza vaccine did not have a

noticeable effect on the odds of pneumonia diagnosis (AOR 1.091, CI 0.632 to 1.884) compared to those who did not receive the influenza vaccine. Among adult, African American patients hospitalized with influenza, those administered antiviral medications had increased odds for the diagnosis of pneumonia (1.963, CI 1.159 to 3.326) compared to those patients who did not receive antiviral medications. The presence of any chronic medical condition among adult, African American patients admitted to a hospital due to influenza did not have a noticeable effect on the odds (AOR 1.448, CI 0616 to 3.402) for the diagnosis of pneumonia during hospitalization compared to similar patients without any chronic underlying medical conditions.

Secondary Analysis of Presenting Symptoms

A secondary analysis of respiratory and non-respiratory symptoms upon illness presentation was conducted to determine if patients with SCD who contract influenza present markedly differently from patients who do not have SCD. Non-respiratory and respiratory symptom data was collected during three influenza seasons; 2014-15, 2015-16 and 2016-17 and includes a total of 42,338 cases of which 4,254 were pediatric cases less than 18 years of age and 38,084 were among adults.

Table 12 summarizes respiratory and non-respiratory symptoms experienced and documented among pediatric patients admitted with laboratory-confirmed influenza by SCD status. Altered mental status (AMS) was documented more often among pediatric patients that did not have SCD (Mean 0.039, CI, 0.028 to 0.050) compared to pediatric patients with SCD (Mean, 0.002, CI, -0.002, to 0.006). Chest pain was reported more frequently among pediatric patients with SCD (Mean 0.212, CI, 0.146 to 0.278) than among pediatric patients without SCD (Mean 0.052, CI, 0.038 to 0.066). Conjunctivitis was experienced more frequently by pediatric patients without SCD (Mean 0.032, CI, 0.020 to 0.045) than by pediatric influenza patients who had SCD (Mean, 0.008, CI 0.000 to 0.016). Diarrhea was reported more often among pediatric patients hospitalized with influenza who did not have SCD (Mean 0.125, CI, 0.106 to 0.144) than among those with SCD (Mean 0.033, CI, 0.011 to 0.056). There was no noticeable

difference in the frequency of fatigue among pediatric patients without SCD (Mean 0.158, CI, 0.132 to 0.184) compared to those with SCD (Mean 0.098, CI, 0.062 to 0.134). Fever was reported more frequently among pediatric patients with SCD who were hospitalized with influenza (Mean 0.904, CI 0.861 to 0.946) than among pediatric patients without SCD (Mean 0.829, CI, 0.803 to 0.855). Headache was recorded in a higher proportion of pediatric patients admitted to a hospital with influenza who had SCD (Mean 0.199, CI, 0.135 to 0.263) than among similar patients without SCD (Mean 0.105, CI 0.087 to 0.124). There was no noticeable difference in the frequency of reports of myalgia experienced by pediatric patients without SCD (Mean 0.111, CI, 0.093 to 0.129) versus pediatric patients with SCD (Mean 0.168, CI, 0.086 to 0.250) admitted with influenza. Nausea was observed more often among pediatric patients without SCD (Mean 0.345, CI, 0.314 to 0.376) than in pediatric patients with SCD (Mean 0.239, CI, 0.174 to 0.304). Skin rash was reported more often among pediatric patients admitted due to influenza that did not have SCD (Mean 0.049, CI 0.037 to 0.061) than in pediatric patients that had SCD (Mean 0.001, CI -0.001 to 0.004). Seizures were reported more often among pediatric patients without SCD (Mean 0.057, CI, 0.044 to 0.070) than among those with SCD (Mean 0.007, CI, -0.007 to 0.021). There was no noticeable difference in the reported frequency of congestion among pediatric patients hospitalized with influenza without SCD (Mean 0.549, CI 0.516 to 0.581) and those with SCD (Mean 0.624, CI, 0.527 to 0.720). Cough was observed in a higher proportion of pediatric patients admitted with influenza who had SCD (Mean 0.854, CI, 0.780 to 0.929) than among patients without SCD (Mean 0.735, CI 0.703 to 0.768). Shortness of breath (SOB) was more commonly reported among pediatric patients without SCD (Mean 0.359, CI, 0.329 to 0.389) than in patients with SCD (Mean 0.166, CI 0.109 to 0.224). Sore throat was observed in more pediatric patients with SCD admitted with influenza (Mean 0.258, CI, 0.173 to 0.342) than in pediatric patients without SCD (Mean 0.131, CI 0.112 to 0.150). Documentation of wheezing was more frequent in pediatric patients without SCD (Mean 0.180, CI, 0.155 to 0.205) than in pediatric patients with SCD (Mean 0.083, CI, 0.034 to 0.131) that were admitted with influenza illness.

Table 13 summarizes respiratory and non-respiratory symptoms experienced and documented among adult patients admitted with laboratory-confirmed influenza by SCD status. AMS was observed at a higher frequency among adult patients admitted with influenza who did not have SCD (Mean 0.164, CI, 0.155 to 0.173) than in adults with SCD (Mean 0.031, CI, -0.015 to 0.076). Chest pain was reported in a higher proportion of adult patients admitted with influenza who had SCD (Mean 0.357, CI, 0.224 to 0.490). Conjunctivitis was observed more frequently in adult patients hospitalized with influenza without SCD (Mean 0.003, CI, 0.002 to 0.004) than patients with SCD (Mean 0.000, CI, 0.000 to 0.000). Diarrhea was documented more often among adult patients without SCD (Mean 0.129, CI, 0.120 to 0.137) than patients with SCD (Mean 0.061, CI, 0.019 to 0.104). Fatigue was observed in a greater proportion of adult patients hospitalized with influenza without SCD (Mean 0.263, CI, 0.246 to 0.280) than in adult patients without SCD (Mean 0.111, CI, 0.029 to 0.193). Fever was more commonly observed in adult patients with SCD (Mean 0.806, CI, 0.713 to 0.900) than in adult patients without SCD (Mean 0.632, CI, 0.618 to 0.647) who were hospitalized with influenza. There was no noticeable difference in the proportion of adult patients who reported headache as part of their influenza illness without SCD (Mean 0.121, CI, 0.110 to 0.132) and those with SCD (0.146, CI, 0.077 to 0.215). Myalgia was observed more often in adults with SCD who were admitted to hospital with influenza (Mean 0.456, CI, 0.314 to 0.599) than in adults without SCD (Mean 0.249, CI, 0.236 to 0.262). There was no noticeable difference in the frequency of nausea reported among adults hospitalized with influenza without SCD (Mean 0.229, CI, 0.217 to 0.240) versus adults with SCD (Mean 0.361, CI, 0.185 to 0.537). Rash was observed rarely but more often in adult patients without SCD (Mean 0.007, CI, 0.005 to 0.010) compared to adults with SCD (Mean 0.000, CI, 0.000 to 0.000) that were hospitalized with influenza. There was no noticeable difference in the reported frequency of seizures in adult patients without SCD (Mean 0.005, CI, 0.003 to 0.007) compared to adult patients with SCD (Mean 0.032, CI, -0.016 to 0.079) who were admitted to a hospital with influenza. There was no noticeable difference in the proportion of adult patients without SCD who experienced congestion (Mean 0.257, CI, 0.245 to 0.269) compared to adult patients with SCD (Mean 0.379, CI, 0.219 to 0.538). Among adult patients hospitalized with influenza, there was no

noticeable difference in the proportion that reported cough in those without SCD (Mean 0.790, CI, 0.777 to 0.803) compared to those with SCD (Mean 0.829, CI 0.753 to 0.906). In adults admitted to a hospital with influenza, those without SCD reported SOB more frequently (Mean 0.576, CI, 0.559 to 0.587) than adults without SCD (Mean 0.294, CI 0.179 to 0.408). There was no noticeable difference in the frequency of sore throat associated with influenza hospitalization between adult patients without SCD (Mean 0.119, CI, 0.110 to 0.127) and similar patients with SCD (Mean 0.203, CI, 0.120 to 0.285). Similarly, no noticeable difference in the reported frequency of wheezing was observed in adult patients without SCD (Mean 0.214, CI, 0.202 to 0.225) and adults with SCD (Mean 0.037, CI, 0.060 to 0.207) hospitalized with laboratory-confirmed influenza.

Secondary Analysis of Comorbid Conditions

The final analysis presented is an examination of comorbid medical conditions to determine if any are observed more frequently among patients with SCD than among patients without SCD. The frequency and types of comorbid conditions are different among pediatric and adult populations and are presented separately in Table 14 and Table 15.

Table 14 summarizes the estimated frequency of comorbid medical conditions among pediatric patients hospitalized due to influenza by SCD status. Asthma was observed more frequently among pediatric patients hospitalized with influenza and had SCD (Mean 0.358, CI, 0.300 to 0.416) than among those without SCD (Mean 0.251, CI, 0.232, 0.270). There was no noticeable difference in the proportion of pediatric patients hospitalized with influenza and had chronic lung disease and did not have SCD (Mean 0.077, CI, 0.065 to 0.088) and similar patients who had SCD (Mean 0.056, CI, 0.027 to 0.085). No noticeable difference in the estimated frequency of cardiovascular disease was observed among pediatric patients admitted with influenza that did not have SCD (Mean 0.081, CI, 0.070 to 0.093) and those that did have SCD (Mean 0.081, CI, 0048 to 0.114). There was no noticeable difference in the frequency of a previous stroke among pediatric patients hospitalized with influenza without SCD (Mean 0.003, CI, 0.001

to 0.005) and pediatric patients with SCD (Mean 0.021, CI, 0.002 to 0.040). The frequency of diabetes was not noticeably different in pediatric patients without SCD (Mean 0.019, CI, 0.011 to 0.027) than in pediatric patients with SCD (Mean 0.012, CI, -0.013 to 0.037) who were admitted to a hospital due to influenza. Neuromuscular disorders were observed more frequently in pediatric patients without SCD (Mean 0.035, CI, 0.004 to 0.026) compared to pediatric patients with SCD (Mean 0.005, CI, -0.002 to 0.011). Similarly, neurological disorders were observed in a higher proportion of pediatric patients hospitalized with influenza that did not have SCD (Mean, 0.171, CI, 0.154 to 0.188) than among those with SCD (Mean 0.055, CI, 0.020 to 0.090). Immunosuppressive conditions were more frequency observed in pediatric patients without SCD (Mean 0.099, CI, 0.081 to 0.116) than pediatric patients with SCD (0.048, CI, 0.07 to 0.080). In pediatric patients admitted with influenza, renal disease was observed more often patients without SCD (Mean 0.032, CI, 0.022 to 0.042) than in those with SCD (Mean 0.007, CI, -0.003 to 0.017). Among pediatric patients hospitalized with influenza, there was no noticeable difference in the frequency of liver disease in those without SCD (Mean 0.004, CI, 0.002 to 0.006) and those with SCD (Mean 0.001, CI, -0.001 to 0.004). There was also no noticeable difference in the reported frequency of current smoking among pediatric patients admitted with influenza among those without SCD (Mean 0.002, CI, 0.001 to 0.003) and those with SCD (Mean, 0.005, CI, 0.000 to 0.010). There was no documented alcohol abuse among pediatric patients admitted for influenza.

Table 15 summarizes the estimated frequency of comorbid medical conditions among adult patients hospitalized due to influenza by SCD status. In this population, there was no noticeable difference in the frequency of asthma as an underlying condition among adults without SCD (Mean 0.303, CI, 0.286 to 0.321) and those with SCD (Mean 0.289, CI, 0.201 to 0.377). Chronic lung disease was observed in a higher proportion of adult patients without SCD who were admitted with influenza (Mean 0.140, CI, 0.124 to 0.156) than among adult patients with SCD (Mean 0.044, CI, 0.016 to 0.072). No noticeable difference in the frequency of cardiovascular disease among adult patients without SCD (Mean 0.137, CI, 0.147 to 0.186) and adults with SCD (Mean 0.247, CI, 0.143 to 0.351) was observed. There was no noticeable difference in the proportion previously documented stroke in adult patients

hospitalized with influenza who did not have SCD (Mean 0.023, CI, 0.018 to 0.029) and those without SCD (Mean 0.033, CI, 0.008 to 0.057). No noticeable difference in the proportion of adult patients with diabetes was observed among those without SCD (Mean 0.180, CI, 0.168 to 0.193) and those with SCD (Mean 0.114, CI, 0.019 to 0.210). Neuromuscular disorders were observed more frequently in adult patients hospitalized with influenza without SCD (Mean 0.041, CI, 0.033 to 0.050) than among similar patients with SCD (Mean 0.013, CI, 0.000 to 0.026). There was no noticeable difference in the proportion of patients with neurological disorders among adult patients hospitalized due to influenza and did not have SCD (Mean 0.154, CI, 0.137 to 0.171) compared to those with SCD (Mean 0.133, CI, 0.040 to 0.226). There was no noticeable difference in the proportion patients with immunosuppressive conditions among adult patients hospitalized due to influenza and did not have SCD (Mean 0.178, CI, 0.164 to 0.193) versus similar patients with SCD (Mean 0.150, CI 0.049 to 0.251). There was no noticeable difference in the proportion of patients with renal disease among adult patients hospitalized due to influenza and did not have SCD (Mean 0.088, CI, 0.078 to 0.099) and those with SCD (Mean 0.079, CI, 0.030 to 0.127). Among adults hospitalized with influenza, the proportion of patients with liver disease was greater among those without SCD (Mean 0.036, CI, 0.029 to 0.043) than among those with SCD (Mean 0.010, CI, -0.002 to 0.021). In adults admitted to a hospital with influenza, there was no noticeable difference in the proportion of current smoking in those without SCD (Mean 0.330, CI, 0.314 to 0.347) and those with SCD (0.287, CI, 0.170 to 0.404). Lastly, in adult patients hospitalized with influenza, no noticeable difference was observed in the proportion of patients currently abusing alcohol in those without SCD (Mean 0.052, CI, 0.042 to 0.061) compared to those with SCD (Mean 0.022, CI, -0.013 to 0.057).

Summary of Hypothesis Conclusions

A review of the research questions, associated hypotheses and the conclusions reached based on this analysis follows and is also summarized in Table 16.

The first research question focused on the frequency of prevention and treatment measures in patients with SCD compared to those without SCD. Hypothesis 1.1 posited that the proportion of patients with SCD who received influenza vaccine would be the same as the proportion of patients without SCD who received the influenza vaccine. This hypothesis would be rejected. Among pediatric patients hospitalized with influenza, those with SCD were more likely to have received an influenza vaccine than patients without SCD. The same result was observed in an analysis restricted to pediatric, African American patients, a higher proportion of those with SCD received vaccine than patients without SCD. The null hypothesis would also be rejected in the analysis of adult patients hospitalized with influenza of all races where it was observed those without SCD received an influenza vaccine more frequently than those with SCD. In African American adult patients, the null hypothesis cannot be rejected as there is no noticeable difference in the proportion of patients who received influenza vaccine between patients with SCD and those without SCD.

Hypothesis 1.2 proposed patients with SCD and patients without SCD were equally likely to have received antiviral treatment during influenza-related hospitalizations. This hypothesis would be rejected in pediatric patients of all races where it was observed that patients with SCD were more likely to receive antiviral treatment during hospitalization compared to patients without SCD. The hypothesis holds among adult patients of all races, patients with and without SCD received antiviral medications at the same frequency. Hypothesis 2 would be accepted for pediatric and adult African American patients hospitalized with influenza. In both age groups, patients with SCD and those without SCD, the same proportion of patients received antiviral therapy during hospitalization.

The second research question pertained to the risk of influenza-related outcomes of ICU admission and pneumonia among patients with SCD compared to those without SCD. Hypothesis 2.1, hospitalized influenza patients with SCD no greater risk for admission to an ICU during their hospital stay than hospitalized influenza patients without SCD, is rejected in all cases because this analysis showed patients with SCD hospitalized due to influenza had lower risk of ICU admission than patients

without SCD. The results were the same in pediatric and adult patients of all races as well as in pediatric and adult patients among only African American patients.

Similarly, hypothesis 2.2, hospitalized influenza patients with SCD have no greater risk of a diagnosis of pneumonia at discharge than hospitalized influenza patients without SCD, can be rejected in all scenarios as well. Consistently, patients with SCD had lower risk for the development of pneumonia than patients without SCD during influenza hospitalization. These conclusions were found in pediatric and adult patients of all races as well as in analysis restricted to pediatric and adult patients of African American race.

The third research question outlines the secondary analysis of this study related to the presentation of symptoms and associated underlying comorbid conditions in patients with SCD hospitalized with influenza versus patients without SCD. Hypothesis 3.1, hospitalized influenza patients with SCD are no more likely to report respiratory or non-respiratory symptoms at the time of hospitalization than influenza patients without SCD, is rejected since there are differences in symptoms associated with influenza illness among patients with SCD compared to those without SCD. Chest pain, fever, headache, cough and sore throat were reported more frequently in pediatric patients with SCD hospitalized with influenza than patients without SCD. Chest pain and fever were the only symptoms more frequently reported by adults with SCD compared to adults without SCD that were hospitalized with influenza. Therefore, this hypothesis is rejected in these cases. Regarding other symptoms, they were reported as frequently in patients with and without SCD or less frequently by patients with SCD compared to those without SCD.The final hypothesis, hospitalized influenza patients with SCD are no more likely to have underlying medical conditions than hospitalized influenza patients without SCD, is rejected in pediatric patients where asthma was found to be more common among patients with SCD than those without SCD hospitalized with influenza. All other comorbid conditions were reported less frequently or with the same frequency in patients with SCD versus patients without SCD.

Table 2

Frequency of laboratory-confirmed, hospitalized cases of influenza and proportion of sickle cell disease by FluSurv-NET study site among pediatric and adult cases

	Pediatric Cases (<18 years)			Adult Cases (18 years and older)		
FluSurv-NET Site	Cases	# SCD +	% SCD +	Cases	# SCD +	% SCD +
California	652	22	3.37	6,695	13	0.19
Colorado	1,042	12	1.15	5,540	14	0.25
Connecticut	212	15	7.08	4,335	26	0.60
Georgia	1,006	122	12.13	4,592	41	0.89
Maryland	781	88	11.27	6,427	40	0.62
Michigan	385	12	3.12	1,397	11	0.79
Minnesota	980	36	3.67	6,506	15	0.23
New Mexico	418	1	0.24	1,768	2	0.11
New York	549	33	6.01	7,025	34	0.48
Ohio	442	34	7.69	3,823	23	0.60
California	216	2	0.93	3,735	7	0.19
Tennessee	264	9	3.41	2,852	13	0.46
Utah	459	5	1.09	2,332	2	0.09
Total	7,406	391	5.28	57,027	241	0.42

Abbreviations: SCD, sickle cell disease

Table 3

Frequency of laboratory-confirmed, hospitalized cases of influenza and proportion of sickle cell disease by FluSurv-NET study site among all ages and adult cases aged 18-49 years

	All Cases			Adult cases (18-49 years)		
FluSurv-NET Site	Cases	# SCD +	% SCD +	Cases	# SCD +	% SCD +
California	7,347	35	0.48	1,019	13	1.3
Colorado	6,582	26	0.40	1,054	14	1.3
Connecticut	4,547	41	0.90	716	26	3.6
Georgia	5,598	163	2.91	1,338	41	3.1
Maryland	7,208	128	1.78	1,278	40	3.1
Michigan	1,782	23	1.29	273	11	4.0
Minnesota	7,486	51	0.68	1,087	15	1.4
New Mexico	2,186	3	0.14	372	2	0.5
New York	7,574	67	0.88	1,214	34	2.8
Ohio	4,265	57	1.34	884	23	2.6
California	3,951	9	0.23	608	7	1.2
Tennessee	3,116	22	0.71	623	13	2.1
Utah	2,791	7	0.25	594	2	0.3
Total	64,433	632	0.98	11,084	241	2.2

Abbreviations: SCD, sickle cell disease

Table 4

Frequency of laboratory-confirmed, hospitalized cases of influenza and proportion of sickle cell disease by gender and age group

Gender	# of Influenza Cases	# SCD +	% SCD +
All ages			
Female	34,808	335	0.96
Male	29,625	297	1.0
Pediatric cases			
Female	3,247	182	5.6
Male	3,950	209	5.0
Adult cases			
Female	31,561	153	0.48
Male	25,378	88	0.35

Abbreviations: SCD, sickle cell disease

Table 5

Frequency of laboratory-confirmed, hospitalized cases of influenza and proportion of sickle cell disease by age group

Age Group	Frequency	Proportion of Total Cases	SCD #	% SCD +
<6 months	1,189	1.8	19	1.60%
6 months - 17 years	6,230	9.7	372	5.97%
18 - 49 years	11,083	17.2	202	1.82%
50 - 64 years	13,336	20.7	25	0.19%
65+ years	32,595	50.6	14	0.04%

Abbreviations: SCD, sickle cell disease

Table 6

Immunization, clinical intervention and outcome of individuals hospitalized with laboratory-confirmed influenza among pediatric (<18 years) and adult (≥18 years) patients by SCD status

Pediatric Patients								
	SCD -				SCD +			
			95% CLM				95% CLM	
Intervention / Event	Mean	SEM	Low	High	Mean	SEM	Low	High
Vaccine	0.399	0.012	0.375	0.422	0.549	0.02	0.51	0.589
Antiviral	0.738	0.017	0.703	0.773	0.841	0.025	0.791	0.891
Bacterial Infection	0.019	0.003	0.013	0.025	0.005	0.003	0.000	0.010
PNA	0.174	0.009	0.156	0.193	0.061	0.013	0.035	0.088
ICU admission	0.200	0.011	0.179	0.222	0.051	0.015	0.021	0.080
Mechanical Vent	0.056	0.005	0.046	0.066	0.006	0.004	-0.001	0.014
Death	0.010	0.002	0.006	0.015	0	0	0	0

Adult Patients								
	SCD -				SCD +			
			95% CLM				95% CLM	
Intervention / Event	Mean	SEM	Low	High	Mean	SEM	Low	High
Vaccine	0.540	0.006	0.529	0.551	0.442	0.031	0.380	0.504
Antiviral	0.844	0.008	0.829	0.859	0.880	0.036	0.808	0.953
Bacterial Infection	0.036	0.003	0.031	0.041	0.014	0.007	-0.001	0.028
PNA	0.231	0.005	0.222	0.241	0.117	0.032	0.053	0.182
ICU admission	0.182	0.005	0.171	0.193	0.088	0.02	0.048	0.128
Mechanical Vent	0.078	0.003	0.072	0.084	0.013	0.008	-0.004	0.030
Death	0.038	0.002	0.034	0.042	0.002	0.002	-0.002	0.005

Abbreviations: SCD, sickle cell disease; Vaccine, seasonal influenza immunization received; Antiviral, antiviral medication received during hospitalization; Bacterial Infection, bacterial infection from a sterile or respiratory site; PNA, diagnosis of pneumonia; ICU, intensive care unit; Mechanical Vent, mechanical ventilation required

Table 7

Immunization, clinical intervention and outcome of individuals hospitalized with laboratory-confirmed influenza among African American pediatric (<18 years) and adult (≥18 years) patients by SCD status

Pediatric Patients								
	SCD -				SCD +			
			95% CLM				95% CLM	
Intervention / Event	Mean	SEM	Low	High	Mean	SEM	Low	High
Vaccine	0.374	0.039	0.297	0.451	0.631	0.049	0.533	0.730
Antiviral	0.783	0.025	0.734	0.832	0.840	0.038	0.763	0.917
Bacterial Infection	0.020	0.006	0.008	0.031	0.009	0.007	-0.004	0.022
PNA	0.219	0.030	0.159	0.280	0.069	0.015	0.040	0.098
ICU admission	0.171	0.023	0.125	0.217	0.062	0.028	0.006	0.117
Mechanical Vent	0.055	0.011	0.033	0.076	0.016	0.007	0.001	0.030
Death	0.012	0.006	0.001	0.023	0.000	0.000	0.000	0.000

Adult Patients								
	SCD -				SCD +			
			95% CLM				95% CLM	
Intervention / Event	Mean	SEM	Low	High	Mean	SEM	Low	High
Vaccine	0.542	0.019	0.504	0.580	0.476	0.069	0.339	0.613
Antiviral	0.831	0.014	0.802	0.860	0.902	0.033	0.835	0.969
Bacterial Infection	0.040	0.006	0.028	0.052	0.006	0.004	-0.001	0.013
PNA	0.236	0.011	0.214	0.258	0.099	0.041	0.016	0.182
ICU admission	0.204	0.012	0.180	0.227	0.089	0.038	0.014	0.164
Mechanical Vent	0.091	0.008	0.074	0.107	0.020	0.015	-0.009	0.049
Death	0.041	0.004	0.033	0.050	0.003	0.003	-0.003	0.008

Abbreviations: SCD, sickle cell disease; Vaccine, seasonal influenza immunization received; Antiviral, antiviral medication received during hospitalization; Bacterial Infection, bacterial infection from a sterile or respiratory site; PNA, diagnosis of pneumonia; ICU, intensive care unit; Mechanical Vent, mechanical ventilation required

Table 8

Logistic Regression of ICU admission (dependent variable) in pediatric and adult patients admitted to a hospital with laboratory confirmed influenza, all races

	ICU Admission Pediatric Cases (<18 years)				ICU Admission Adult cases (≥18 years)			
		95% CI				95% CI		
Patient Characteristics	AOR	Low	High	P-Value	AOR	Low	High	P-Value
Had SCD (vs. No)	0.120	0.061	0.226	<0.0001	0.236	0.159	0.351	<0.0001
Male Gender (vs. Female)	0.900	0.731	1.110	0.320	1.172	1.087	1.264	<0.0001
Age (5 years)	1.240	1.093	1.409	0.001	0.966	0.956	0.975	<0.0001
Race								
White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.491	1.115	1.995	0.001	0.908	0.802	1.027	0.775
Other	0.862	0.578	1.284	0.169	0.901	0.776	1.046	0.900
Unknown	0.973	0.704	1.345	0.498	0.781	0.640	0.953	0.074
Ethnicity								
Non-Hispanic	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Hispanic	0.861	0.575	1.288	0.417	1.181	0.856	1.629	0.381
Unknown	1.004	0.751	1.343	0.579	1.063	0.924	1.209	0.798
Received Influenza Vaccine (Vs. No)	1.003	0.853	1.180	0.972	0.871	0.814	0.932	0.000
Received Antiviral Treatment (Vs. No)	2.089	1.536	2.842	<0.0001	1.469	1.255	1.720	<0.0001
Had Chronic Medical Condition (Vs. No)	1.198	0.978	1.467	0.080	1.675	1.364	2.056	<0.0001

Abbreviations: SCD, sickle cell disease, ICU, intensive care unit, Influenza vaccine, seasonal influenza vaccine received at least 2 weeks prior to admission, Antiviral treatment, antiviral medication received during hospitalization, Medical Condition, patient was document to have at least one underlying comorbid condition besides sickle cell disease.

Table 9

Logistic Regression of diagnosis of pneumonia (dependent variable) in pediatric and adult patients admitted to a hospital with laboratory confirmed influenza, all races

	Pneumonia Diagnosis Pediatric Cases (<18 years)				Pneumonia Diagnosis Adult cases (≥18 years)			
		95% CI				95% CI		
Patient Characteristics	AOR	Low	High	P-Value	AOR	Low	High	P-Value
Had SCD (vs. No)	0.233	0.129	0.420	<0.0001	0.407	0.255	0.648	0.000
Male Gender (vs. Female)	0.780	0.601	1.013	0.062	1.221	1.121	1.331	<0.0001
Age (5 years)	0.961	0.858	1.104	0.678	1.015	1.005	1.025	0.011
Race								
White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.342	0.993	1.813	0.017	0.882	0.774	1.005	0.081
Other	1.214	0.756	1.950	0.268	1.207	1.015	1.435	0.001
Unknown	0.662	0.436	1.005	0.006	0.812	0.703	0.938	0.004
Ethnicity								
Non-Hispanic	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Hispanic	1.624	0.905	2.916	0.044	1.357	1.134	1.624	0.001
Unknown	0.940	0.687	1.287	0.024	1.001	0.896	1.118	0.017
Received Influenza Vaccine (Vs. No)	1.028	0.869	1.216	0.746	0.913	0.862	0.968	0.003
Received Antiviral Treatment (Vs. No)	1.773	1.377	2.284	<0.0001	1.202	1.075	1.345	0.002
Had Chronic Medical Condition (Vs. No)	0.855	0.689	1.061	0.153	0.838	0.683	1.030	0.091

Abbreviations: SCD, sickle cell disease, ICU, intensive care unit, Influenza vaccine, seasonal influenza vaccine received at least 2 weeks prior to admission, Antiviral treatment, antiviral medication received during hospitalization, Medical Condition, patient was document to have at least one underlying comorbid condition besides sickle cell disease.

Table 10

Logistic Regression of ICU admission (dependent variable) in pediatric and adult patients admitted to a hospital with laboratory-confirmed influenza, African American race

	ICU Admission Pediatric Cases (<18 years)				ICU Admission Adult cases (≥18 years)			
		95% CI				95% CI		
Patient Characteristics	AOR	Low	High	P-Value	AOR	Low	High	P-Value
Had SCD (vs. No)	0.066	0.012	0.349	0.002	0.167	0.058	0.480	0.001
Male Gender (vs. Female)	2.441	1.078	5.525	0.033	2.095	1.199	3.662	0.010
Age (5 years)	1.409	0.778	2.551	0.251	0.909	0.850	0.970	0.005
Ethnicity								
Non-Hispanic	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Hispanic	0.312	0.067	1.454	0.733	1.575	0.227	10.94	0.476
Unknown	0.159	0.044	0.576	0.046	0.550	0.295	1.022	0.234
Received Influenza Vaccine (Vs. No)	2.192	0.893	5.384	0.085	1.276	0.772	2.108	0.336
Received Antiviral Treatment (Vs. No)	2.009	0.571	7.066	0.270	2.384	1.312	4.330	0.005
Had Chronic Medical Condition (Vs. No)	2.510	1.238	5.090	0.012	2.122	1.028	4.380	0.042

Abbreviations: SCD, sickle cell disease, ICU, intensive care unit, Influenza vaccine, seasonal influenza vaccine received at least 2 weeks prior to admission, Antiviral treatment, antiviral medication received during hospitalization, Medical Condition, patient was document to have at least one underlying comorbid condition besides sickle cell disease.

Table 11

Logistic Regression of pneumonia diagnosis (dependent variable) in pediatric and adult patients admitted to a hospital with laboratory-confirmed influenza, African American race

	Pneumonia Diagnosis Pediatric Cases (<18 years)				Pneumonia Diagnosis Adult cases (≥18 years)			
		95% CI				95% CI		
Patient Characteristics	AOR	Low	High	P-Value	AOR	Low	High	P-Value
Had SCD (vs. No)	0.052	0.012	0.217	0.000	0.205	0.067	0.630	0.006
Male Gender (vs. Female)	1.169	0.323	4.238	0.808	1.393	0.761	2.550	0.277
Age (5years)	1.700	0.828	3.480	0.144	0.941	0.859	1.030	0.174
Ethnicity								
Non-Hispanic	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Hispanic	0.122	0.025	0.591	0.025	0.300	0.107	0.837	0.066
Unknown	0.503	0.185	1.364	0.511	0.496	0.303	0.810	0.674
Received Influenza Vaccine (Vs. No)	2.210	0.877	5.564	0.091	1.091	0.632	1.884	0.750
Received Antiviral Treatment (Vs. No)	4.312	1.694	10.98	0.003	1.963	1.159	3.326	0.013
Had Chronic Medical Condition (Vs. No)	1.056	0.399	2.793	0.911	1.448	0.616	3.402	0.390

Abbreviations: SCD, sickle cell disease, ICU, intensive care unit, Influenza vaccine, seasonal influenza vaccine received at least 2 weeks prior to admission, Antiviral treatment, antiviral medication received during hospitalization, Medical Condition, patient was document to have at least one underlying comorbid condition besides sickle cell disease.

Table 12

Symptoms associated with laboratory-confirmed, hospitalized influenza cases among pediatric patients (<18 year) by sickle cell disease status

	SCD -				SCD +			
			95% CLM				95% CLM	
Symptoms	**Mean**	**SEM**	**Low**	**High**	**Mean**	**SEM**	**Low**	**High**
AMS	0.039	0.005	0.028	0.050	0.002	0.002	-0.002	0.006
Chest Pain	0.052	0.007	0.038	0.066	0.212	0.033	0.146	0.278
Conjunctivitis	0.032	0.006	0.020	0.045	0.008	0.004	0.000	0.016
Diarrhea	0.125	0.010	0.106	0.144	0.033	0.011	0.011	0.056
Fatigue	0.158	0.013	0.132	0.184	0.098	0.018	0.062	0.134
Fever	0.829	0.013	0.803	0.855	0.904	0.021	0.861	0.946
Headache	0.105	0.009	0.087	0.124	0.199	0.032	0.135	0.263
Myalgia	0.111	0.009	0.093	0.129	0.168	0.041	0.086	0.250
Nausea	0.345	0.016	0.314	0.376	0.239	0.032	0.174	0.304
Rash	0.049	0.006	0.037	0.061	0.001	0.001	-0.001	0.004
Seizure	0.057	0.006	0.044	0.070	0.007	0.007	-0.007	0.021
Congestion*	0.549	0.016	0.516	0.581	0.624	0.048	0.527	0.720
Cough*	0.735	0.016	0.703	0.768	0.854	0.037	0.780	0.929
SOB*	0.359	0.015	0.329	0.389	0.166	0.029	0.109	0.224
Sore Throat*	0.131	0.009	0.112	0.150	0.258	0.042	0.173	0.342
Wheeze*	0.180	0.013	0.155	0.205	0.083	0.024	0.034	0.131

Abbreviations: SCD, sickle cell disease, AMS, altered mental status, SOB, shortness of breath, SEM, standard error of the mean, CLM, confidence limit of the mean
*respiratory symptoms

Table 13

Symptoms upon Hospitalization of Influenza Cases by Sickle Cell Disease Status, Adult Cases, ≥18 years

	SCD -				SCD +			
			95% CLM				95% CLM	
Symptom	**Mean**	**SEM**	**Low**	**High**	**Mean**	**SEM**	**Low**	**High**
AMS	0.164	0.005	0.155	0.173	0.031	0.023	-0.015	0.076
Chest Pain	0.163	0.006	0.151	0.176	0.357	0.067	0.224	0.490
Conjunctivitis	0.003	0.000	0.002	0.004	0.000	0.000	0.000	0.000
Diarrhea	0.129	0.004	0.120	0.137	0.061	0.021	0.019	0.104
Fatigue	0.263	0.009	0.246	0.280	0.111	0.041	0.029	0.193
Fever	0.632	0.007	0.618	0.647	0.806	0.047	0.713	0.900
Headache	0.121	0.006	0.110	0.132	0.146	0.035	0.077	0.215
Myalgia	0.249	0.006	0.236	0.262	0.456	0.072	0.314	0.599
Nausea	0.229	0.006	0.217	0.240	0.361	0.088	0.185	0.537
Rash	0.007	0.001	0.005	0.010	0.000	0.000	0.000	0.000
Seizure	0.005	0.001	0.003	0.007	0.032	0.024	-0.016	0.079
Congestion*	0.257	0.006	0.245	0.269	0.379	0.080	0.219	0.538
Cough*	0.790	0.007	0.777	0.803	0.829	0.038	0.753	0.906
SOB*	0.573	0.007	0.559	0.587	0.294	0.057	0.179	0.408
Sore Throat*	0.119	0.004	0.110	0.127	0.203	0.041	0.120	0.285
Wheeze*	0.214	0.006	0.202	0.225	0.133	0.037	0.060	0.207

Abbreviations: SCD, sickle cell disease, AMS, altered mental status, SOB, shortness of breath, SEM, standard error of the mean, CLM, confidence limit of the mean
*respiratory symptoms

Table 14

Frequency of comorbid conditions among pediatric cases of laboratory-confirmed, hospitalized influenza by sickle cell disease status

	SCD -				SCD +			
			95% CLM				95% CLM	
Comorbid Condition	Mean	SEM	Low	High	Mean	SEM	Low	High
Asthma	0.251	0.0096	0.232	0.270	0.358	0.0289	0.300	0.416
CLD	0.077	0.0059	0.065	0.088	0.056	0.0146	0.027	0.085
CVD	0.081	0.0057	0.070	0.093	0.081	0.0166	0.048	0.114
Stroke	0.003	0.0009	0.001	0.005	0.021	0.0096	0.002	0.040
Diabetes	0.019	0.0039	0.011	0.027	0.012	0.0124	-0.013	0.037
Neuromuscular disorder	0.035	0.0044	0.026	0.044	0.005	0.0033	-0.002	0.011
Neurological disorder	0.171	0.0085	0.154	0.188	0.055	0.0176	0.020	0.090
Immunosuppressed	0.099	0.0089	0.081	0.116	0.048	0.0158	0.017	0.08
Renal disease	0.032	0.0052	0.022	0.042	0.007	0.005	-0.003	0.017
Liver disease	0.004	0.0009	0.002	0.006	0.001	0.0013	-0.001	0.004
Current smoker	0.002	0.0006	0.001	0.003	0.005	0.0025	0	0.01
Alcohol abuse	0	0	0	0	0	0	0	0

Abbreviations; SCD, sickle cell disease, CLD, chronic lung disease, CVD, cardiovascular disease, Smoker, current smoker, SEM, standard error of the mean, CLM, confidence limit of the mean

Table 15

Frequency of comorbid conditions among adult cases of laboratory-confirmed, hospitalized influenza by sickle cell disease Status

	SCD -				SCD +			
			95% CLM				95% CLM	
Comorbid Condition	Mean	SEM	Low	High	Mean	SEM	Low	High
Asthma	0.303	0.0088	0.286	0.321	0.289	0.0442	0.201	0.377
CLD	0.140	0.008	0.124	0.156	0.044	0.014	0.016	0.072
CVD	0.167	0.0098	0.147	0.186	0.247	0.052	0.143	0.351
Stroke	0.023	0.0028	0.018	0.029	0.033	0.0121	0.008	0.057
Diabetes	0.180	0.0064	0.168	0.193	0.114	0.0477	0.019	0.21
Neuromuscular disorder	0.041	0.0044	0.033	0.050	0.013	0.0065	0	0.026
Neurological disorder	0.154	0.0083	0.137	0.171	0.133	0.0465	0.040	0.226
Immunosuppressed	0.178	0.0072	0.164	0.193	0.15	0.0507	0.049	0.251
Renal Disease	0.088	0.0054	0.078	0.099	0.079	0.0243	0.030	0.127
Liver Disease	0.036	0.0036	0.029	0.043	0.01	0.0057	-0.002	0.021
Smoker	0.330	0.0083	0.314	0.347	0.287	0.0585	0.170	0.404
Alcohol abuse	0.052	0.0047	0.042	0.061	0.022	0.0174	-0.013	0.057

Abbreviations; SCD, sickle cell disease, CLD, chronic lung disease, CVD, cardiovascular disease, Smoker, current smoker, SEM, standard error of the mean, CLM, confidence limit of the mean

Table 16

Summary of null hypotheses and conclusions to accept or reject each hypothesis

	Patients of all races		African American Patients	
Null Hypothesis	Pediatric (<18 years)	Adult (≥18 years)	Pediatric (<18 years)	Adult (≥18 years)
H1: There is no difference in proportion of vaccine receipt between hospitalized influenza patients with SCD and influenza patients without SCD.	Reject	Reject	Reject	Accept
H2: There is no difference in proportion of antiviral treatmetn between hospitalized influenza patients with SCD and hospitalized influenza patients without SCD.	Reject	Accept	Accept	Accept
H3: Hospitalized influenza patients with SCD have no greater risk for admission to an ICU during their hospital stay than hospitalized influenza patients without SCD.	Reject	Reject	Reject	Reject
H4: Hospitalized influenza patients with SCD have no greater risk of a diagnosis of pneumonia at discharge than hospitalized influenza patients without SCD.	Reject	Reject	Reject	Reject
H5: There is no difference in proportion of respiratory or non-respiraotry symptoms between hospitalized influenza patients with SCD and influenza patients without SCD.	Reject*	Reject**	NA	NA
H6: There is no difference in proportion of underlying comorbid medical conditiosn between hospitalized influenza patients with SCD and hospitalized influenza patients without SCD.	Reject***	Accept	NA	NA

*Chest pain, fever, headache, cough and sore throat were more common in patients with SCD
**Chest pain and fever were more common in adults with SCD
*** Asthma in pediatric patients was more reported more often in pediatric patients with SCD

CHAPTER 5

DISCUSSION

Summary of Findings

This study sets out to answer three research questions: 1) among patients hospitalized with influenza, is there variation in intervention or treatment between patients with sickle-cell disease and those without sickle-cell diseases? 2) do individuals with SCD who are hospitalized with influenza have an increased risk of severe outcomes during hospitalization such as admission to an ICU or diagnosis of pneumonia compared to individuals without SCD hospitalized with influenza? 3) among patients hospitalized with influenza, are there differences in clinical symptoms at presentation and comorbid underlying conditions between patients with sickle-cell disease and those without sickle-cell disease?

The estimated proportion of pediatric patients with documented receipt of annual influenza vaccine was significantly higher among those with SCD (Mean, 0.549, CI 0.51 to 0.589) than those without SCD (Mean, 0.399, CI, 0.375 to 0.422). Among adult patients, the opposite was observed; the estimated proportion of patients that received annual influenza immunization before an influenza-related hospitalization was greater among those without SCD (Mean, 0.540, CI, 0.529 to 0.551) compared to adults with SCD (Mean, 0.442, CI, 0.380 to 0.504). The administration of antiviral medications was common regardless of patient age or SCD status. Nevertheless, among pediatric patients that required hospital admission from influenza illness, the proportion of pediatric patients with SCD that received antiviral medication was higher (Mean 0.841, CI, 0.791 to 0.891) compared to those without SCD (Mean 0.738, CI, 0.0703 to 0.773). Among adults admitted with influenza, there was no noticeable difference in the proportion who received antiviral medication during hospitalization between those with SCD (Mean, 0.880, CI, 0.808 and 0.953) and those without SCD (Mean, 0.844, CI, 0.829 to 0.859).

A parallel analysis was conducted among only African American patients to evaluate any association only due to SCD absent of any racial influence. Among pediatric African American patients, those with SCD had a higher proportion who received an annual influenza vaccine before hospitalization

with influenza (Mean, 0.631, CI, 0.533 to 0.730) than similar patients without SCD (Mean 0.374, CI, 0.297 to 0.451). In adult African American patients hospitalized with influenza, there was no noticeable difference in the proportion of patients who received an influenza vaccine before hospitalization among those with SCD (Mean 0.476, CI, 0.339 to 0.613) versus those without SCD (Mean 0.542, CI, 0.504 to 0.580). There was no noticeable difference in the proportion of pediatric African American patients admitted to a hospital with influenza who received antiviral treatment between those with SCD (Mean 0.840, CI, 0.763 to 0.917) and those without SCD (Mean 0.783, CI, 0.734 to 0.832). Similarly, no noticeable difference in the proportion of adult African American patients who received antiviral medications was observed between those with SCD (Mean 0.902, CI, 0.835 to 0.969) versus those without SCD (Mean 0.831, CI, 0.802 to 0.860).

In adult and pediatric patients of all races as well as among African American adult and pediatric patients hospitalized with influenza, those with SCD received influenza vaccine and antiviral treatment at least as frequently, if not more frequently than similar patients without SCD.

The second research question was an assessment of the risk associated with SCD for the development of severe outcomes during influenza-related hospitalizations. In both pediatric and adult patients admitted to a hospital with influenza, the odds of admission to an ICU was lower in patients with SCD (AOR 0.120, CI, 0.061 to 0.226) compared to those without SCD. Similar results were observed among adult patients hospitalized with influenza; those with SCD had lower odds for ICU admission than those without SCD (AOR, 0.236, CI, 0.159 to 0.351). Likewise, the odds for the diagnosis of pneumonia during influenza-related hospitalizations was lower among pediatric (AOR 0.233, CI, 0.129 to 0.420) and adult patients (AOR 0.407, CI, 0.255 to 0.648) with SCD than pediatric or adult patients without SCD, respectively.

A parallel analysis was conducted to evaluate the associated risk of SCD for influenza complications among African American patients admitted to a hospital with influenza. The odds of ICU admission among African America pediatric (AOR 0.066, CI, 0.012 to 0.349) and adult (AOR 0.167, CI, 0.058 to 0.480) patients with SCD was lower than among African American pediatric and adult patients

without SCD. Similarly, the odds of the diagnosis of pneumonia among African America pediatric (AOR 0.052, CI, 0.012 to 0.217) and adult (AOR 0.205, CI, 0.067 to 0.630) patients with SCD were lower than among African American pediatric and adult patients without SCD.

Individuals with SCD consistently had lower risk of ICU admission and diagnosis of pneumonia than patients without SCD among patients hospitalized due to influenza infection. Of note, receipt of antiviral treatment during influenza-related hospitalization indicated increased odds for ICU admission and diagnosis of pneumonia. This association was observed in pediatric and adult patients of all races (Tables 8 and 9). This association was also observed in African American adult patients for ICU admission and pneumonia diagnosis and diagnosis of pneumonia among pediatric African American patients though not for ICU admission in pediatric African American patients.

Among pediatric patients hospitalized with influenza, African American patients had increased risk for ICU admission (AOR 1.491, CI 1.115 to 1.995) and diagnosis of pneumonia (AOR 1.342, CI 0.993 to 1.813) compared to Caucasian patients though this was only statistically significant for ICU admission. In adult patients of all races, males had greater odds for admission to ICU (AOR 1.172, CI 1.087 to 1.264) and diagnosis of pneumonia (AOR 1.221, CI 1.121 to 1.331) during influenza-related hospitalizations compared to females. Among adult patients hospitalized with influenza, receipt of influenza vaccine before hospital admission was shown to lower odds of ICU admission (AOR 0.871, CI 0.814 to 0.932) and pneumonia diagnosis (AOR 0.913, CI 0.862 to 0.968) though this effect was not noticeable in pediatric patients. Other patient characteristics showed no or an inconsistent effect on the odds for ICU admission and diagnosis of pneumonia across logistic regression models.

Lastly, the study examined symptoms upon presentation to a hospital as well as the frequency of other comorbid medical conditions to determine if patients with SCD present differently with influenza compared to patients without SCD. Regarding the presentation of symptoms, chest pain and fever were the only two symptoms reported more frequently by both pediatric and adult patients with SCD compared to their respective counterparts without SCD. Myalgia was reported by a higher proportion of adult

patients with SCD than adults without SCD hospitalized with flu but this was not observed among pediatric cases.

As for chronic, underlying medical conditions, asthma was the only comorbid condition observed more frequently among patients with SCD than those without SCD and that was only among pediatric patients that were admitted to a hospital with influenza illness.

Literature Comparison

Previous literature on influenza among patients with SCD is limited to a few studies. Two studies report elevated rates of hospitalization among pediatric patients with SCD (Bundy et al., 2010; Inusa et al., 2010) compared to those without SCD. Data obtained from FluSurv-NET and analyzed in the current study agrees with these previous studies. It is estimated that 1 in 100,000 individuals in the United States have SCD. However, approximately, 5.3% of pediatric FluSurv-NET cases and 0.4% of adult cases had documented SCD as an underlying condition, a higher proportion than expected given 1 in 100,000 individuals living with SCD.

An analysis of pediatric patients with SCD hospitalized in London during the 2009 H1N1 pandemic indicated 25% of these patients experienced ACS (Inusa et al., 2010). Though FluSurv-NET does not document instances of ACS, symptoms were collected for three years of the study. Chest pain, cough and fever, symptoms observed during ACS episodes, were reported more frequently in pediatric patients with SCD than those without SCD in the FluSurv-NET and chest pain and cough were observed more frequently in adult patients with SCD compared to those without SCD signaling a high rate of ACS among patients with SCD identified by FluSurv-NET. This is consistent with previous findings acute chest syndrome is often the result of a bacterial or viral infection (NIH, 2002).

The 2009 H1N1 influenza A subtype was demonstrated to be more severe than seasonal influenza strains among patients with SCD (Strouse et al., 2010). FluSurv-NET data were not analyzed in this manner since the focus of this analysis was patients with SCD compared to those without SCD.

Among patients hospitalized with influenza, length of stay, costs and outcomes were shown to not be any more or more severe for pediatric patients with SCD than those without ((Bundy et al., 2010). The length of hospital stay was not assessed in this analysis and costs could not be estimated given the available data. Based on the analyzed FluSurv-NET data, patients with SCD consistently had lower odds for ICU admission or diagnosis of pneumonia compared to individuals without SCD. These results were observed in pediatric and adult patients of all races and among pediatric and adult African Americans. Of note, previous studies have focused on pediatric populations. This study provides initial evidence that adult patients with SCD are not at increased risk of severe outcomes during influenza-related hospitalization.

Implications

The central finding of this study was among individuals hospitalized with influenza, patients with SCD had lower risk of ICU admission and pneumonia diagnosis than patients without SCD. Additionally, influenza vaccine coverage among peditric patients with SCD was greater than among patients without SCD. However, this later finding was not observed in adult patients. Despite these findings, improvements in influenza vaccine coverage can still be made among individuals with SCD as well as among those who do not have SCD.

The proportion of patients with documented immunization before hospitalization ranged from 39.9% among pediatric patients without SCD to 63.1% among African American pediatric patients with SCD. These results are similar to estimated influenza vaccine coverage from the entire United States from the same six-year period which ranged from 41.8% in 2011-12 to 46.8% in 2016-17. Healthy People 2020 has stated goals of 80% influenza vaccine coverage among pediatric populations and 90% among those with at-risk comorbid conditions such as SCD (ODPHP, 2019) indicating influenza vaccine coverage in patients with and without SCD fell far short of these goals.

Transforming this data into public health practice requires focusing on specific data from this study and other studies that indicate increased risk of hospitalization for patients with SCD from influenza. Primarily, individuals with SCD are hospitalized at much higher rates due to influenza infection than individuals without SCD. Secondly, the models produced in this study containing patients of all races, influenza vaccine was shown to reduce the odds of ICU admission as well as diagnosis of pneumonia. This needs to be a central point of education for patients with SCD, that even if vaccination fails to prevent illness and hospitalization, it still decreases likelihood of severe outcomes. It is around these two facets that future guidance for individuals with SCD and hemotologists should revolve.

Despite universal influenza vaccine recommendations and availabilty of influenza vaccine at physician offices, employers, pharmacies and grocery stores, vaccine uptake lags for numerous reasons includeing vaccine misconceptions, missed opportunities by healthcare workers (Lu, O'Halloran, Ding, Srivastav, & Williams, 2016) and a lack of perceived risk by patients (Freimuth et al., 2017). Even among pediatric patients hospitalized during the influenza season, nearly half the parents refused the influenza vaccine for their hospitalized child (Cameron, Bigos, Festa, Topol, & Rhee, 2016). Therefore, targeted information needs to be developed for hematologists and family physicians to increase vaccine coverage among individuals with SCD, particularly adults where coverage lags behind those without SCD according to results from this study.

This information should be part of training information or clinical decision tools geared towards increasing the competancy of family physicians, a knowledge gap indicated by family physicians. Supplemental information could also be provided to hematologists and hospital-based physicians practicing in communities with significant African American and Hispanic populations where seeing patients with SCD is likely to occur. Information should be tailored for each respective setting but include information regarding vaccine safety, facts to combat common vaccine misconceptions, and goals of vaccination which include prevention of illness, hospitalization and severe influenza-related outcomes, providing full disclosure that no vaccine is entirely effective but influenza vaccine attenuates illness (M. G. Thompson et al., 2018). Household members living with an individual with SCD should also be

targeted for influenza immunizaiton to provide another layer of influenza transmission. The goal would be to increase vaccine uptake by removing barriers among patients and family members, decreasing missed opportunities of vaccination by hematologists, family physicians and hospital-based physicians to prevent unnecessary influenza-related hospitalizations among individuals with SCD.

Limitations

There were a few limitations in this study. First, FluSurv-NET gathers information on laboratory-confirmed, hospitalized patients with influenza. Several external and unpredictable factors may influence the detection and inclusion of patients into this surveillance system. The likelihood of being tested for influenza may differ depending on the hospital of presentation, treating physicians or due to differences in local practices from one surveillance site to another. Additionally, even if tested, the likelihood of testing positive for influenza also depends on the laboratory test used by each hospital. It has been shown that rapid influenza diagnostic tests (RIDT) are less sensitive compared to molecular-based methods (Merckx et al., 2017) for the detection of influenza. The decision to admit a patient depends on their perceived risk which is a factor of both their current acute illness and contribution of underlying comorbid conditions. In other words, individuals with comorbid conditions may be more likely to be admitted to a hospital given the same level of symptom presentation as an otherwise healthy individual. Taken together, biases may exist related to patient inclusion within this surveillance system. One example would be the preferential inclusion of patients from hospitals with sufficient resources to test all patients suspected of having influenza compared to resource-poor hospitals who may only test patients perceived to be severely ill.

Another limitation of the analysis presented here is related to adult patients. Few individuals over fifty years of age had SCD. Among all adults, there were 57,027 cases of influenza reported in the six years of surveillance from the FluSurv-NET program, 11,083 of them, or 19.4%, of which were aged 18-49 years. However, 202 of 241 or 83.4% of adults with SCD were between the ages of 18 and 49. The comparisons made here involved adults of all ages. Therefore, younger adults with SCD were compared

to older adults. Three of twelve chronic comorbid conditions were more frequent among patients without SCD than among those with SCD including chronic lung disease, neuromuscular disorder, and liver disease.

Another limitation of this study is a lack of information related to each patient's SCD and current treatment since the surveillance system was designed to collect information related to influenza illness and not in-depth data related to underlying conditions. SCD is caused by an assortment of multiple genetic mutations, some more severe than others. The specific form of SCD was not collected for each patient enrolled in the study. Also of interest would be knowing if patients with SCD were currently on regular antibiotic regimen, recommended for patients under five, or if they were receiving hydroxyurea treatment.

Nevertheless, the analyses conducted were between patients with SCD and those without SCD though patients in both groups may have other more severe comorbid underlying conditions. Comparing individuals with SCD against patients with other, potentially more severe comorbid conditions may not be as appropriate as a comparison against patients with no underlying conditions or patients with a condition such as asthma which may have a similar threshold for admission as patients presenting with influenza and have SCD.

Lastly, the population under FluSurv-NET surveillance may not represent the United States population. Study sites were selected were selected through competitive awards with consideration of racial and ethnic composition but local catchment areas were also selected based on convenience and available resources and site capabilities.

Recommendations

Using the coceptual model presented earlier, there are several recommendations for future research to explore the effect of influenza upon individuals with SCD. Efforts should be made to estimate and correct for missed cases. Influenza testing practices including type of test used and insufficient testing

frequency per hospital bases could lead to differential assessment of cases and incomplete identification of influenza cases among individuals with SCD paricularly if hospitals serving predominantly African American patients are resource-poor and lack adequate funds for comprehensive influenza testing.

Since FluSurv-NET is a surveillance system designed to assess influenza hospitalizaiton rates, it does not collect data outside of this scope. To further explore influenza among patients with SCD, there are other data that would be of interest to collect including insurance coverage at time of hospitalization, hydroxyurea regimen status and among children under five years of age, penicillin regimen. Inclusion of these data would provide additional information related to proportion of patients with SCD receiving recommended care and allow analysis to determine if these measures have benefit to those receiving them.

Since individuals with SCD transition from pediatric care to adult care during ages 16 – 25 years of age, future analysis among adult patients should be conducted in an age-restricted group of 25 to 49 years of age. This would capture the majority of individuals with SCD hospitalized with influenza and avoid inclusion of a large number of older adults who have other severe underlying conditions. Another consideration would be comparing patients with SCD to either patients hospitalized who lack comborbid condition or another underlying condition which may have a similar threshold for hospital admission, perhaps asthma.

Lastly, FluSurv-NET data could be used to corroborate one study that found SCD patients infected with 2009 H1N1 had worse outcomes than patients infected with seasonal H3N2 influenza (Strouse et al., 2010). FluSurv-NET does collect obtain influenza sub-type data on a subset of observed cases. If sufficient influenza sub-type data exists, FluSurv-NET data could be used to confirm this result.

Conclusions

The major finding of this study is that among individuals hospitalized with laboratory-confirmed influenza infections, patients with SCD do not have an increased risk of ICU admission or diagnosis of

pneumonia compared to individuals without SCD. These findings are consistent with previous research that pediatric patients with SCD are at increased risk for hospitalization from influenza but do not experience longer hospitalization, incur greater costs or have more severe outcomes than patients without SCD. This study provides initial evidence that adult patients with SCD hospitalized due to influenza also do not experience more severe outcomes than patients without SCD.

Encouragingly, pediatric patients with SCD were more likely to receive an annual influenza vaccine compared to patients without SCD. However, this was not observed among adult patients. More importantly, influenza vaccination rates were well below Healthy People 2020 goals. The continued effort needs to be directed to increasing the annual uptake of influenza vaccine to prevent and mitigate seasonal influenza outbreaks for those vaccinated and to protect immunocompromised individuals and individuals unable to receive the influenza vaccine.

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APPENDIX A

GEORGIA SOUTHERN UNIVERSITY IRB APPROVAL LETTER

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PO Box 8005
Statesboro, GA 30460

To: Openo, Kyle P.; Shah, Gulzar

From: Office of Research Services and Sponsored Programs
Administrative Support Office for Research Oversight Committees (IACUC/IBC/IRB)

Approval Date: 7/16/2018

Subject: Status of Application for Approval to Utilize Human Subjects in Research

After a review of your proposed research project numbered **H18433,** titled **"Epidemiology, Clinical Features and Outcomes of Hospitalized Sickle-Cell Disease Patients With Influenza,"** it appears that your research involves activities that do not require full approval by the Institutional Review Board (IRB) according to federal guidelines. In this research project research data will be collected anonymously.

According to the Code of Federal Regulations Title 45 Part 46, your research protocol is determined to be exempt from full review under the following exemption category(s):

B4 Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Any alteration in the terms or conditions of your involvement may alter this approval. *Therefore, as authorized in the Federal Policy for the Protection of Human Subjects, I am pleased to notify you that your research, as submitted, is exempt from IRB approval. You will be asked to notify the IRB upon project completion. If you alter the project, it is your responsibility to notify the IRB and acquire a new determination of exemption.*

Sincerely,

Eleanor Haynes
Research Integrity Officer

APPENDIX B

FLUSURV-NET 2015-16 CASE REPORT FORM

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
ATLANTA, GA 30333

2015-16 FluSurv-NET Influenza Hospitalization Surveillance Project Case Report Form

Form Approved
OMB No. 0920-0978

Case ID: 1 5 1 6

A. Patient Data – THIS INFORMATION IS NOT SENT TO CDC

Last Name: _____ First Name: _____ Chart Number: _____

Address: _____ (Number, Street, Apt. No.) Census Tract: _____ Address Type: _____

_____ (City) _____ (State) _____ (Zip Code) Emergency Contact 1: _____

Phone No.1: _____ Phone No.2: _____ Emergency Contact Phone: _____

PCP Name 1: _____ PCP Phone 1: _____ PCP Fax 1: _____

PCP Name 2: _____ PCP Phone 2: _____ PCP Fax 2: _____

Site Use 1: _____ Site Use 2: _____ Site Use 3: _____

B. Reporter Information – THIS INFORMATION IS NOT SENT TO CDC

1. Reporter Name: _____ 2. Date Reported: ____/____/____

C. Enrollment Information

1. Case Classification: ☐ Prospective Surveillance ☐ Discharge Audit

2. Admission Type: ☐ Hospitalization ☐ Observation Only

3. County:

4. State:

5. Case Type: ☐ Pediatric ☐ Adult

6. Date of Birth: ____/____/____

7. Age: _____ ☐ Years ☐ Days (if < 1 month) ☐ Months (if < 1 yr)

8. Sex: ☐ Female ☐ Male

9. Race: ☐ White ☐ Black or African American ☐ Asian/Pacific Islander ☐ American Indian or Alaska Native ☐ Multiracial ☐ Not specified

10. Ethnicity: ☐ Hispanic or Latino ☐ Non-Hispanic or Latino ☐ Not Specified

11. Hospital ID Where Patient Treated: _____

11a. Admission Date: ____/____/____

11b. Discharge Date: ____/____/____

12. Was patient transferred from another hospital? ☐ Yes ☐ No ☐ Unknown

12a. Transfer Hospital ID: _____

12b. Transfer Hospital Admission Date: ____/____/____

12c. Transfer Date: ____/____/____

13. Where did patient reside at the time of hospitalization? (Indicate TYPE of residence.)

☐ Private residence ☐ Homeless/Shelter ☐ Nursing home ☐ Alcohol/Drug Abuse Treatment ☐ Hospitalized at birth ☐ Rehabilitation facility ☐ Jail/Prison ☐ Hospice ☐ Assisted living/Residential care ☐ LTACH/Transitional Care (TCU) ☐ Group home/Retirement home ☐ Mental Hospital ☐ Unknown ☐ Other, specify: _____

13a. If resident of a facility, indicate NAME of facility: _____

D. Influenza Testing Results

1. Test 1: ☐ Rapid ☐ Molecular Assay ☐ Viral Culture ☐ Serology ☐ Fluorescent Antibody ☐ Method Unknown/Note Only

1a. Result: ☐ Flu A (no subtype) ☐ 2009 H1N1 ☐ H1, Unspecified ☐ H3 ☐ Flu A, Unsubtypable ☐ Flu B (no genotype) ☐ Flu B, Victoria ☐ Flu B, Yamagata ☐ Flu A & B ☐ Flu A/B (Not Distinguished) ☐ Unknown Type ☐ Negative ☐ Other, specify: _____

1b. Specimen collection date: ____/____/____ **1c. Testing facility ID:** _____ **1d. Specimen ID:** _____

2. Test 2: ☐ Rapid ☐ Molecular Assay ☐ Viral Culture ☐ Serology ☐ Fluorescent Antibody ☐ Method Unknown/Note Only

2a. Result: ☐ Flu A (no subtype) ☐ 2009 H1N1 ☐ H1, Unspecified ☐ H3 ☐ Flu A, Unsubtypable ☐ Flu B (no genotype) ☐ Flu B, Victoria ☐ Flu B, Yamagata ☐ Flu A & B ☐ Flu A/B (Not Distinguished) ☐ Unknown Type ☐ Negative ☐ Other, specify: _____

2b. Specimen collection date: ____/____/____ **2c. Testing facility ID:** _____ **2d. Specimen ID:** _____

3. Test 3: ☐ Rapid ☐ Molecular Assay ☐ Viral Culture ☐ Serology ☐ Fluorescent Antibody ☐ Method Unknown/Note Only

3a. Result: ☐ Flu A (no subtype) ☐ 2009 H1N1 ☐ H1, Unspecified ☐ H3 ☐ Flu A, Unsubtypable ☐ Flu B (no genotype) ☐ Flu B, Victoria ☐ Flu B, Yamagata ☐ Flu A & B ☐ Flu A/B (Not Distinguished) ☐ Unknown Type ☐ Negative ☐ Other, specify: _____

3b. Specimen collection date: ____/____/____ **3c. Testing facility ID:** _____ **3d. Specimen ID:** _____

4. Test 4: ☐ Rapid ☐ Molecular Assay ☐ Viral Culture ☐ Serology ☐ Fluorescent Antibody ☐ Method Unknown/Note Only

4a. Result: ☐ Flu A (no subtype) ☐ 2009 H1N1 ☐ H1, Unspecified ☐ H3 ☐ Flu A, Unsubtypable ☐ Flu B (no genotype) ☐ Flu B, Victoria ☐ Flu B, Yamagata ☐ Flu A & B ☐ Flu A/B (Not Distinguished) ☐ Unknown Type ☐ Negative ☐ Other, specify: _____

4b. Specimen collection date: ____/____/____ **4c. Testing facility ID:** _____ **4d. Specimen ID:** _____

2015-16 FluSurv-NET Influenza Hospitalization Surveillance Project Case Report Form

Case ID: _____ 1 5 1 6 _____

E. Admission and Patient History

1. Was patient discharged from any hospital within one week prior to the current admission date? ☐ Yes ☐ No ☐ Unknown

2. Acute signs/symptoms at admission *(within 2 weeks prior to positive flu test)*: *(Write Y or N/Unk next to signs/symptoms)*

____ Altered mental status/confusion	____ Cough*	____ Headache	____ Seizures	____ Wheezing*
____ Chest pain	____ Diarrhea	____ Myalgia/muscle aches	____ Shortness of breath/resp distress*	____ Other, non-respiratory
____ Congested/runny nose*	____ Fatigue/weakness	____ Nausea/vomiting	____ Sore throat*	
____ Conjunctivitis/pink eye	____ Fever/chills	____ Rash	____ URI/ILI*	

3. Date of onset of acute respiratory symptoms *(within 2 weeks prior to positive flu test)*: ____ /____ /____ ☐ Unknown

4. Date of onset of acute condition resulting in current hospitalization: ____ /____ /____ ☐ Unknown

5. BMI: _____	6. Height: _____	7. Weight: _____	8. Smoker:	9. Alcohol abuse:
☐ Unknown	☐ In ☐ Cm ☐ Unknown	☐ Lbs ☐ Kg ☐ Unknown	☐ Current ☐ Former ☐ No/Unknown	☐ Current ☐ Former ☐ No/Unknown

10. Did patient have any of the following pre-existing medical conditions? Check all that apply. ☐ Yes ☐ No ☐ Unknown

10a. Asthma/Reactive Airway Disease? ☐ Yes ☐ No/Unknown

10b. Chronic Lung Disease? ☐ Yes ☐ No/Unknown
- ☐ Cystic fibrosis
- ☐ Emphysema/COPD
- ☐ Other, specify: _____

10c. Chronic Metabolic Disease ☐ Yes ☐ No/Unknown
- ☐ Diabetes Mellitus
- ☐ Thyroid dysfunction
- ☐ Other, specify: _____

10d. Blood disorders/Hemoglobinopathy ☐ Yes ☐ No/Unknown
- ☐ Sickle cell disease
- ☐ Splenectomy/Asplenia
- ☐ Thrombocytopenia
- ☐ Other, specify: _____

10e. Cardiovascular Disease ☐ Yes ☐ No/Unknown
- ☐ Atherosclerotic cardiovascular disease (ASCVD)
- ☐ Atrial Fibrillation
- ☐ Cerebral vascular incident/Stroke
- ☐ Congenital heart disease
- ☐ Coronary artery disease (CAD)
- ☐ Heart failure/CHF
- ☐ Other, specify: _____

10f. Neuromuscular disorder ☐ Yes ☐ No/Unknown
- ☐ Duchenne muscular dystrophy
- ☐ Muscular dystrophy
- ☐ Multiple sclerosis
- ☐ Mitochondrial disorder
- ☐ Myasthenia gravis
- ☐ Other, specify: _____

10g. Neurologic disorder ☐ Yes ☐ No/Unknown
- ☐ Cerebral palsy
- ☐ Cognitive dysfunction
- ☐ Dementia
- ☐ Developmental delay
- ☐ Down syndrome
- ☐ Plegias/Paralysis
- ☐ Seizure/Seizure disorder
- ☐ Other, specify: _____

*These are considered acute respiratory symptoms

10h History of Guillain-Barré Syndrome ☐ Yes ☐ No/Unknown

10i. Immunocompromised Condition ☐ Yes ☐ No/Unknown
- ☐ AIDS or CD4 count < 200
- ☐ Cancer: current/in treatment or diagnosed in last 12 months
- ☐ Complement deficiency
- ☐ HIV Infection
- ☐ Immunoglobulin deficiency
- ☐ Immunosuppressive therapy
- ☐ Organ transplant
- ☐ Stem cell transplant (e.g., bone marrow transplant)
- ☐ Steroid therapy (taken within 2 weeks of admission)
- ☐ Other, specify: _____

10j. Renal Disease ☐ Yes ☐ No/Unknown
- ☐ Chronic kidney disease/chronic renal insufficiency
- ☐ End stage renal disease/Dialysis
- ☐ Glomerulonephritis
- ☐ Nephrotic syndrome
- ☐ Other, specify: _____

10k. Other ☐ Yes ☐ No/Unknown
- ☐ Intravenous drug use
- ☐ Liver disease (e.g., cirrhosis, chronic hepatitis, hepatitis C)
- ☐ Systemic lupus erythematosus/SLE/Lupus
- ☐ Morbidly obese (ADULTS ONLY)
- ☐ Obese
- ☐ Pregnant
  - ☐ If pregnant, specify gestational age in weeks: _____
  - ☐ Unknown gestational age
- ☐ Post-partum (two weeks or less)
- ☐ Other, specify: _____

10l. PEDIATRIC CASES ONLY

Abnormality of upper airway ☐ Yes ☐ No/Unknown

History of febrile seizures ☐ Yes ☐ No/Unknown

Long-term aspirin therapy ☐ Yes ☐ No/Unknown

Premature ☐ Yes ☐ No/Unknown
(gestation age < 37 weeks at birth for patients < 2yrs)
If yes, specify gestational age at birth in weeks: _____
☐ Unknown gestational age at birth

F. Intensive Care Unit and Interventions

1. Was the patient admitted to an intensive care unit (ICU)? ☐ Yes ☐ No ☐ Unknown

1a. Number of ICU admissions: _____ ☐ Unknown

1b. Date of first ICU Admission: ____ /____ /____ ☐ Unknown

1c. Date of first ICU Discharge: ____ /____ /____ ☐ Unknown

2. Did patient receive mechanical ventilation? ☐ Yes ☐ No ☐ Unknown

3. Did patient receive extracorporeal membrane oxygenation (ECMO or 'on bypass')? ☐ Yes ☐ No ☐ Unknown

2015-16 FluSurv-NET Influenza Hospitalization Surveillance Project Case Report Form

Case ID: _____ 1 5 1 6 _____

G. Bacterial Pathogens – *Sterile or respiratory site only*

1. Were any bacterial culture tests performed with a collection date within three days of admission? ☐ Yes ☐ No ☐ Unknown

2. If yes, was there a positive culture for a bacterial pathogen? ☐ Yes ☐ No ☐ Unknown

3a. If yes, specify Pathogen 1: _____

3b. Date of culture: ____/____/____

3c. Site where pathogen identified:
☐ Blood ☐ Cerebrospinal fluid (CSF)
☐ Bronchoalveolar lavage (BAL) ☐ Sputum
☐ Pleural fluid ☐ Endotracheal aspirate
☐ Other, specify: _____

3d. If Staphylococcus aureus, specify:
☐ Methicillin resistant (MRSA) ☐ Methicillin sensitive (MSSA) ☐ Sensitivity unknown

3e. If Haemophilus influenzae, specify if type B:
☐ Yes ☐ No ☐ Unknown

3f. If Neisseria meningitidis, specify serogroup:
☐ B ☐ C ☐ Y
☐ Other, specify: _____ ☐ Unknown

4a. If yes, specify Pathogen 2: _____

4b. Date of culture: ____/____/____

4c. Site where pathogen identified:
☐ Blood ☐ Cerebrospinal fluid (CSF)
☐ Bronchoalveolar lavage (BAL) ☐ Sputum
☐ Pleural fluid ☐ Endotracheal aspirate
☐ Other, specify: _____

4d. If Staphylococcus aureus, specify:
☐ Methicillin resistant (MRSA) ☐ Methicillin sensitive (MSSA) ☐ Sensitivity unknown

4e. If Haemophilus influenzae, specify if type B:
☐ Yes ☐ No ☐ Unknown

4f. If Neisseria meningitidis, specify serogroup:
☐ B ☐ C ☐ Y
☐ Other, specify: _____ ☐ Unknown

H. Viral Pathogens

1. Was patient tested for any of the following viral respiratory pathogens within 3 days of admission? ☐ Yes ☐ No ☐ Unknown

1a. Respiratory syncytial virus/RSV	☐ Yes, positive	☐ Yes, negative	☐ Not tested/Unknown	Date: ____/____/____
1b. Adenovirus	☐ Yes, positive	☐ Yes, negative	☐ Not tested/Unknown	Date: ____/____/____
1c. Parainfluenza 1	☐ Yes, positive	☐ Yes, negative	☐ Not tested/Unknown	Date: ____/____/____
1d. Parainfluenza 2	☐ Yes, positive	☐ Yes, negative	☐ Not tested/Unknown	Date: ____/____/____
1e. Parainfluenza 3	☐ Yes, positive	☐ Yes, negative	☐ Not tested/Unknown	Date: ____/____/____
1f. Parainfluenza 4	☐ Yes, positive	☐ Yes, negative	☐ Not tested/Unknown	Date: ____/____/____
1g. Human metapneumovirus	☐ Yes, positive	☐ Yes, negative	☐ Not tested/Unknown	Date: ____/____/____
1h. Rhinovirus/Enterovirus	☐ Yes, positive	☐ Yes, negative	☐ Not tested/Unknown	Date: ____/____/____
1i. Coronavirus (type):_____	☐ Yes, positive	☐ Yes, negative	☐ Not tested/Unknown	Date: ____/____/____

I. Influenza Treatment

1. Did patient receive antiviral medication treatment for influenza during the course of this illness? ☐ Yes ☐ No ☐ Unknown

2a. Treatment 1: ☐ Oseltamivir (Tamiflu) ☐ Zanamivir (Relenza) ☐ Other, specify: _____
☐ Amantadine (Symmetrel) ☐ Rimantadine (Flumadine) ☐ Unknown

2b. Method of Administration: ☐ Oral ☐ Intravenous (IV) ☐ Inhaled ☐ Unknown

2c. Start Date: ____/____/____ ☐ Start Date Unknown
2d. End Date: ____/____/____ ☐ End Date Unknown
2e. Dose: _____ ☐ Dose Unknown
2f. Frequency: _____ ☐ Frequency Unknown

3a. Treatment 2: ☐ Oseltamivir (Tamiflu) ☐ Zanamivir (Relenza) ☐ Other, specify: _____
☐ Amantadine (Symmetrel) ☐ Rimantadine (Flumadine) ☐ Unknown

3b. Method of Administration: ☐ Oral ☐ Intravenous (IV) ☐ Inhaled ☐ Unknown

3c. Start Date: ____/____/____ ☐ Start Date Unknown
3d. End Date: ____/____/____ ☐ End Date Unknown
3e. Dose: _____ ☐ Dose Unknown
3f. Frequency: _____ ☐ Frequency Unknown

4a. Treatment 3: ☐ Oseltamivir (Tamiflu) ☐ Zanamivir (Relenza) ☐ Other, specify: _____
☐ Amantadine (Symmetrel) ☐ Rimantadine (Flumadine) ☐ Unknown

4b. Method of Administration: ☐ Oral ☐ Intravenous (IV) ☐ Inhaled ☐ Unknown

4c. Start Date: ____/____/____ ☐ Start Date Unknown
4d. End Date: ____/____/____ ☐ End Date Unknown
4e. Dose: _____ ☐ Dose Unknown
4f. Frequency: _____ ☐ Frequency Unknown

5a. Treatment 4: ☐ Oseltamivir (Tamiflu) ☐ Zanamivir (Relenza) ☐ Other, specify: _____
☐ Amantadine (Symmetrel) ☐ Rimantadine (Flumadine) ☐ Unknown

5b. Method of Administration: ☐ Oral ☐ Intravenous (IV) ☐ Inhaled ☐ Unknown

5c. Start Date: ____/____/____ ☐ Start Date Unknown
5d. End Date: ____/____/____ ☐ End Date Unknown
5e. Dose: _____ ☐ Dose Unknown
5f. Frequency: _____ ☐ Frequency Unknown

6. Additional Treatment Comments:

2015-16 FluSurv-NET Influenza Hospitalization Surveillance Project Case Report Form

Case ID: _____ 1 5 1 6 _____

J. Chest Radiograph – *Based on radiology report only*

1. Was a chest x-ray taken *within 3 days* of admission? ☐ Yes ☐ No ☐ Unknown

2. Were any of these chest x-rays abnormal? ☐ Yes ☐ No ☐ Unknown

2a. Date of first abnormal chest x-ray: _____ /_____ /_____

2b. For first abnormal chest x-ray, please check all that apply:

- ☐ Report not available
- ☐ Air space density/opacity
- ☐ Bronchopneumonia/pneumonia
- ☐ Cannot rule out pneumonia
- ☐ Consolidation
- ☐ Atelectasis
- ☐ Cavitation
- ☐ ARDS (acute respiratory distress syndrome)
- ☐ Interstitial infiltrate
- ☐ Pleural effusion/empyema
- ☐ Lobar infiltrate
- ☐ Other

K. Discharge Summary

1. Did the patient have any of the following diagnoses at discharge? (check all that apply)

Pneumonia	☐ Yes ☐ No ☐ Unknown	Stroke (CVI)	☐ Yes ☐ No ☐ Unknown
Guillain-Barré syndrome	☐ Yes ☐ No ☐ Unknown	Acute myocarditis	☐ Yes ☐ No ☐ Unknown
Acute encephalopathy/ encephalitis	☐ Yes ☐ No ☐ Unknown	Acute respiratory distress syndrome (ARDS)	☐ Yes ☐ No ☐ Unknown
Seizures	☐ Yes ☐ No ☐ Unknown	Bronchiolitis	☐ Yes ☐ No ☐ Unknown
Reye's syndrome	☐ Yes ☐ No ☐ Unknown	Hemophagocytic syndrome	☐ Yes ☐ No ☐ Unknown

2. What was the outcome of the patient?

- ☐ Alive
- ☐ Deceased
- ☐ Unknown

2a. If discharged alive, please indicate to where:

- ☐ Private residence
- ☐ Homeless/Shelter
- ☐ Nursing home
- ☐ Alcohol/Drug Abuse Treatment
- ☐ Home with services
- ☐ Rehabilitation Facility
- ☐ Jail/Prison
- ☐ Hospice
- ☐ Assisted living/Residential care
- ☐ LTACH/Transitional Care (TCU)
- ☐ Group home/Retirement home
- ☐ Mental Hospital
- ☐ Unknown
- ☐ Other, specify: _____

3. If patient was pregnant on admission, indicate pregnancy status at discharge: ☐ Still pregnant ☐ No longer pregnant ☐ Unknown

3a. If patient was pregnant on admission but no longer pregnant at discharge, indicate pregnancy outcome at discharge:
☐ Miscarriage ☐ Ill newborn ☐ Newborn died ☐ Healthy newborn ☐ Abortion ☐ Unknown

4. Additional notes regarding discharge:

L. ICD-9 or ICD-10 Discharge Diagnoses – *To be recorded in order of appearance*

Version: ☐ ICD-9 ☐ ICD-10

1. _____ 4. _____ 7. _____
2. _____ 5. _____ 8. _____
3. _____ 6. _____ 9. _____

M. Vaccination History

Specify vaccination status and date(s) by source:

1. Medical Chart:	☐ Yes, full date known	☐ Yes, specific date unknown	☐ No	☐ Unknown	☐ Not Checked
1a. If yes, specify dosage date information:	1) _____ /_____ /_____ ☐ Data Unknown	2) (Pediatrics Only) _____ /_____ /_____ ☐ Data Unknown			
1b. If patient < 9 yrs, specify vaccine type:	☐ Injected Vaccine	☐ Nasal Spray/FluMist	☐ Combination of both	☐ Unknown type	
2. Vaccine Registry:	☐ Yes, full date known	☐ Yes, specific date unknown	☐ No	☐ Unknown	☐ Not Checked
2a. If yes, specify dosage date information:	1) _____ /_____ /_____ ☐ Data Unknown	2) (Pediatrics Only) _____ /_____ /_____ ☐ Data Unknown			
2b. If patient < 9 yrs, specify vaccine type:	☐ Injected Vaccine	☐ Nasal Spray/FluMist	☐ Combination of both	☐ Unknown type	
3. Primary Care Provider / Long-term Care Facility:	☐ Yes, full date known	☐ Yes, specific date unknown	☐ No	☐ Unknown	☐ Not Checked
3a. If yes, specify dosage date information:	1) _____ /_____ /_____ ☐ Data Unknown	2) (Pediatrics Only) _____ /_____ /_____ ☐ Data Unknown			
3b. If patient < 9 yrs, specify vaccine type:	☐ Injected Vaccine	☐ Nasal Spray/FluMist	☐ Combination of both	☐ Unknown type	
4. Interview: ☐ Patient ☐ Proxy	☐ Yes, full date known	☐ Yes, specific date unknown	☐ No	☐ Unknown	☐ Not Checked
4a. If yes, specify dosage date information:	1) _____ /_____ /_____ ☐ Data Unknown	2) (Pediatrics Only) _____ /_____ /_____ ☐ Data Unknown			
4b. If patient < 9 yrs, specify vaccine type:	☐ Injected Vaccine	☐ Nasal Spray/FluMist	☐ Combination of both	☐ Unknown type	

5. If patient < 9 yrs, did patient receive any seasonal influenza vaccine in previous seasons? ☐ Yes ☐ No ☐ Unknown

N. Miscellaneous

1. Additional Comments:

APPENDIX C

FLUSURV-NET 2015-16 PCP VACCINE HISTORY FORM

Date:

Dear **Dr.**

The Georgia Emerging Infections Program, in collaboration with the Georgia Department of Public Health and the Centers for Disease Control and Prevention, are tracking patients who have been hospitalized with influenza. A patient from your clinic, _____ was reported to us as having been hospitalized with influenza beginning on _____. We are trying to obtain immunization history on all hospitalized patients and would appreciate your help in completing the information below for this patient. **If this was not a patient seen by you or another provider at your clinic, please mark "Unknown" for question 1 or 2 below.**

Please fax the completed form to ###-###-####. For any questions, please contact <Study Coordinator>, at ###-###-####. Thank you in advance for your help.

Investigation of these cases falls within the scope of public health surveillance. The Health Insurance Portability and Accountability Act (HIPAA) does NOT prohibit your reporting this information to public health authorities (see http://aspe.hhs.gov/admnsimp/PL104191.htm, Section 1178 (b)).

FOR CHILDREN

1. Did the patient receive the influenza vaccine during fall or winter of the current influenza season? ☐Yes ☐ No ☐ Unknown			
1a. Indicate number of doses: ☐ 1 ☐ 2 ☐ Unknown			
1b. For each dose, specify the date given (mm-dd-yyyy): 1) _____-_____-_____ 2) _____-_____-_____ **1c. If patient < 9 yrs, specify vaccine type:** ☐Injected Vaccine ☐Nasal Spray/FluMist ☐Combination of both ☐Unknown Type			
If patient < 9 years: **2. Did the patient receive influenza vaccine in any previous seasons?** ☐Yes ☐ No ☐ Unknown			
To help us complete the medical information about your patient, could you please provide us with their height and weight if this information was obtained within 6 months before their hospitalization?			
3. HEIGHT: _____ ☐ inches ☐ centimeters		**4. WEIGHT:** _____ ☐ pounds ☐ kilograms	
To help us complete the demographic information about your patient, could you please provide us with their race and ethnicity?			
5. Race (check only one):	☐ White	☐ Black or African American	☐ Asian/Pacific Islander
	☐ Am Indian or Alaska Native	☐ Multiracial	☐ Not specified
6. Ethnicity (check one):	☐ Hispanic or Latino	☐ Non-Hispanic or Latino	☐ Not Specified

APPENDIX D

FLUSURV-NET 2015-16 ADULT VACCINE HISTORY PHONE SCRIPT

CaseID_____ **Birth date:** ___/___/_____
MM/DD/YYYY

FOR ADULT PATIENTS (≥18 YEARS):

Obtain verbal consent, Appendix E, before proceeding.

I'd like to ask you a few questions about _____[patient's name/ child's name]'s vaccination history before [he/she] was hospitalized for influenza or the flu. These questions will take about five minutes to answer.

1. Since August [flu season year], did [you/patient's name] receive a flu shot or flu vaccine? This vaccine is offered every year to protect against the flu.

☐ Yes → go to Q1a

☐ No → If race needed, go to Q2
→ If ethnicity needed, go to Q3
→ If height needed, go to Q4
→ If weight needed, go to Q5
→ If no other information is needed, survey is complete

☐ Unknown
→ If race needed, go to Q2
→ If ethnicity needed, go to Q3
→ If height needed, go to Q4
→ If weight needed, go to Q5
→ If no other information is needed, survey is complete

1a) Can you tell me the date [you/patient's name] received the flu vaccine?

1) _____-_____-_____[MM-DD-YYYY] ☐ Unknown

2) What is [your/patient's name] race? (Check only one)

☐ White
☐ Black or African American
☐ Asian/Pacific Islander
☐ American Indian or Alaska Native
☐ Multiracial
☐ Not specified (refused)
→ If ethnicity needed go to Q3
→ If height needed go to Q4
→ If weight needed go to Q5
→ If neither ethnicity nor height/weight needed, survey is complete

3) What is [your/patient's name] ethnicity?

☐ Hispanic or Latino
☐ Non-Hispanic or Latino
☐ Not Specified (refused to answer)
→ If height/weight needed go to Q3
→ If neither height nor weight is needed survey is complete

4) What is [your/patient's name] height?

HEIGHT: _____ ☐ Inches ☐ Centimeters ☐ Unknown height
→ If weight needed go to Q4
→ If weight not needed survey complete

5) What is [your/patient's name] weight?

WEIGHT: _____☐ Pounds ☐ Kilograms ☐ Unknown weight

THE END. These are all my questions. Do you have any questions for me? [If yes, answer.] Thank you for your time.

APPENDIX E

KEY TO ACRONYMS, ABBREVIATIONS AND SYMBOLS

ACIP = Advisory Committee on Immunization Practices

AIDS = Acquired Immune Deficiency Syndrome

ARDS = Acute Respiratory Distress Syndrome

BMI = Body Mass Index

BRFSS = Behavioral Risk Factor Surveillance Survey

CAD = Coronary Heart Disease

CDC = Centers for Disease Control and Prevention

CDU = Clinical Decision Unit

CHF = Congestive Heart Failure

COPD = Chronic Obstructive Pulmonary Disease

ECMO = Extracorporeal membrane oxygenation

ED = Emergency Department

EIP = Emerging Infections Program

FluSurv-NET = Influenza Hospitalization Surveillance Network

GA-EIP = Georgia Emerging Infections Program

HIV = Human Immunodeficiency Virus

ICU = Intensive Care Unit

ICD-9 = International Classification of Disease, 9^{th} edition

IHSP = Influenza Hospitalization Surveillance Program

IIV = Inactivated Influenza Vaccine

ILI = Influenza-like Illness

LAIV = Live Attenuated Influenza Vaccine

NAIs = Neuraminidase Inhibitors

NIH = National Institutes of Health

SCA = Sickle Cell Anemia

SCD = Sickle Cell Disease

SCMSCD = Self Care Management of Sickle Cell Disease

SES = Socioeconomic Status

SOB = Shortness of Breath

RIDT = Rapid Influenza Diagnostic Test

RNA = Ribonucleic Acid

RT-PCR = Reverse Transcriptase Polymerase Chain Reaction